PART-HUMANS: HOW HUMAN ARE THEY AND DOES IT MATTER?

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Six miles from Reno, Nevada, a flock of sheep gather behind the fence of a farm. Although they look like ordinary sheep, their livers, hearts, brains and other organs contain a large percentage of human cells. In California, human neurons are inserted into mice. In Minnesota, pigs are born with human blood in their veins. These are biologically engineered animals, commonly referred to as "part-humans." The label comes from the assumption that they are neither fully human nor fully nonhuman. Instead, they are a new kind of being. But are animals partially composed of human parts part-human? In my dissertation, I introduce a number of methods available to make this distinction but, upon scrutiny, eliminate each one. Instead, I argue that whether an animal is part-human or merely partially composed of human parts depends on the transposability of parts. A suitably transposable part gives rise to analogous characteristics in both recipient and donor.

The reason why it is important to establish the exact humanness of these animals is because various ethical and legal regulations are grounded in the human/nonhuman distinction, e.g., patenting regulations, regulations for conducting research on human and nonhuman subjects, etc. Hence, my

requirements have practical applications. However, they are only useful insofar as our ethical and legal regulations give preferential treatment to humans over nonhumans. Yet many ethicists—most famously, Peter Singer—have argued against the normative value of the human/nonhuman distinction. Those who oppose giving preferential treatment to humans over nonhumans generally prefer some version of the person/nonperson distinction, where a person has moral status in virtue of having morally relevant characteristics. While it may seem obvious that a proponent of the personhood view ought to find the humanness of part-humans irrelevant to how we ought to judge their moral status, I argue that this need not always be the case. Whether a morally relevant characteristic came about as a result of a human rather than a nonhuman transplant can make a moral difference.

For Matt Mosdell who helped me time and again

when progress seemed hopeless

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CHAPTER 1

INTRODUCTION

Six miles from Reno, Nevada, a flock of sheep gather behind the fence of a farm. Although they look like ordinary sheep, their livers, hearts, brains and other organs contain human cells—some organs as much as 40%. In California, human neurons are inserted into mice. In Minnesota, pigs are born with human blood in their veins. These are biologically engineered animals, commonly referred to as "part-humans" (cf. Hagen & Gittens, 2008; Robert, 2006). The label comes from the assumption that they are neither fully human nor fully nonhuman. Instead, they are a new kind of being. In contrast, consider human patients who have received pig heart-valve transplants. These are humans, partially composed of pig parts, yet no one is assigning them to a new category of being. No one is debating the ethical standing of these patients and certainly no one is referring to them as "part-pig." Is the asymmetry in our understanding of the two cases justified? The answer is not clear because we lack the appropriate method for distinguishing between animals that are merely partially composed of human parts and animals that are part-human.

Why is it important to establish the exact humanness of these animals? The point is not merely to satisfy our curiosity—"It's human! I knew it!"—in the way that our curiosity might be satisfied when we establish the sex of someone with sexually ambiguous characteristics, for example. Although, we may gain satisfaction from establishing just how human these creatures are, the more pressing reason is that various ethical and legal regulations are based on the human/nonhuman distinction. In the United States, for example, research involving human subjects is governed by the Federal Policy for the Protection of Human Subjects, or the "Common Rule" (45 CFR Part 46), and the Institutional Review Board (IRB) is responsible for reviewing and overseeing any research involving human subjects in the academic sphere. Conversely, research involving nonhuman animals is governed by the Animal Welfare Act of 1966 (USC Title 7, Sections 2131 to 2156), which sets the minimum acceptable standard for the treatment of animals in research, exhibition, transport and exchange. In the academic realm, the Institutional Animal Care and Use Committee (IACUC) ensures that nonhuman animals in research are treated humanely. As one might expect, there are major differences between the federal laws and institutional bodies that govern research on human subjects as opposed to nonhuman subjects. For example, even if a study is approved by the IRB, human subjects have to provide informed consent before they can participate. In contrast, the participation of nonhuman subjects is determined solely by

humans, e.g., by the members of the IACUC. In order to put together a research proposal that complies with the relevant regulations, one needs to know if the subject of one's study is human or nonhuman, or perhaps something in between.

Just as academic regulations are grounded on the human/nonhuman distinction, so too are legal regulations—despite the fact that there is no legislation available to help establish what is "human." In 1998, a biotechnology activist, Jeremy Rifkin, and a biology professor, Stuart Newman, brought this problem to the public's attention by filing a patent application for combining human and nonhuman cells to develop a "humanoid" chimera (Rabin, 2006). Chimeras contain cell populations derived from at least two different zygotes. The patent was broadly written, encompassing different human-nonhuman combinations. Rifkin and Newman did not make the chimera, nor did they intend to make one. Instead, they filed the application with the hope of obtaining the patent so that for the 20-year patent term they could prevent other scientists from creating human-nonhuman chimeras.

Under 35 U.S.C. § 101, patents can be granted if the following conditions are met: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title." In the past, the U.S. Supreme

Court has interpreted these regulations broadly to include manmade living things, e.g., microorganisms, plants, animals, etc. that do not appear in nature (Hagglund, 2008). As long as the invention met the requirements, anything made by man was to count as patentable subject matter. Although the Newman-Rifkin patent application met all of the necessary requirements—e.g., the human-nonhuman chimeras were to be made by man, they do not appear in nature, they are nonobvious, etc.—the United States Patent and Trademark Office (USPTO) rejected the Newman-Rifkin application. Members of the Office did not consider human-nonhuman chimeras patentable subject matter because the broadest reasonable interpretation of the invention encompassed a human being and they did not believe that Congress intended for § 101 to include the patenting of humans (Rabin, 2006).

The belief that Congress did not intend for § 101 to include the patenting of humans is supported by that fact that granting exclusive property rights over a human being is prohibited by the Thirteenth Amendment of the U.S. Constitution, which states that "[n]either slavery nor involuntary servitude, except as punishment for crime whereof the party shall have been duly convicted, shall exist within the United States, or any place subject to their jurisdiction" (U.S. Const. amend. XIII, §1). The interpretation of the Thirteenth Amendment has changed significantly over the course of history, although, generally, the interpretations have been fairly

narrowly construed (Goluboff, 2009). In the first half of the 20th century, for example, the Thirteenth Amendment was used to secure the labor and economic rights of African Americans. In the Rifkin-Newman ruling, on the other hand, the Thirteenth Amendment seems to be used more broadly as an argument against the ownership of human beings. Since patents make inventions personal property, a patent on a human would be tantamount to involuntary servitude and thereby unconstitutional.

The problem with the Rifkin-Newman ruling is its apparent inconsistency with past rulings. In recent years, the USPTO has granted patents on human cell lines as well as on microorganisms and multicellular organisms containing a limited number of human genes. If the USPTO granted patents on "humanoid" organisms in the past, why reject the Rifkin-Newman patent application? Members of the USPTO have admitted that they lack a principled way of deciding which human-nonhuman combinations are more human than others. As Deputy Commissioner John Doll commented, "I don't think anyone knows in terms of crude percentages [of human genetic material] how to differentiate between humans and nonhumans" (Weiss, 2005, p. A03). Instead, members of the USPTO expect the legislative branch to provide guidelines as to what is and is not human.

What we have seen, then, is that various ethical and legal regulations are based on the human/nonhuman distinction. This is why it is important to establish the degree to which nonhuman animals composed of human parts

are human. Of course, establishing what it takes to be human in the age of advancing biotechnology is no longer as simple as establishing that one is the offspring of two human parents. Today, the cellular and genetic lineages comprising an individual may have multiple origins. Consequently, defining what it means to be human is a difficult task. However, instead of categorically deciding what is and is not human, a less intimidating task—yet one that will nonetheless bring us closer to sorting out the humanness of these creatures—is to establish criteria for eliminating animals as contenders. In this way, we can establish which animals we need not worry about and which deserve to be considered in more detail. This is the primary aim of my dissertation: to establish the minimum that is required for an animal to count as part-human, i.e., an animal in need of a closer look, as opposed to an animal that is merely partially composed of human parts, i.e., an animal that we need not worry about.

What I argue is that transferred human parts have to be integrated into the animal in a way that would make it possible for them to give rise to human characteristics. Otherwise, the animal is merely composed of human parts. Thus, for example, a shark that eats an entire human being would be a case that does not meet this minimum requirement. Although the shark now contains all the parts required to make a human being in its digestive system, these parts are not integrated in a way that would make it possible for them to give rise to human characteristics. Hence, we would not consider

this shark part-human. Consequently, we can put it in the category of animals that we need not worry about. The same verdict would apply to mice that have human ovaries implanted under the surface of their skin, or so I will argue. While there might be other reasons to worry about such experiments, e.g., the welfare of the animal, cost-benefit analysis, etc., the point is that we need not worry about the *human status* of these animals.

What I offer, then, has obvious practical applications. Research ethics committees and members of the USPTO can use my requirements to set aside submissions that involve animals partially composed of human parts so that they can dedicate more time to the part-human candidates. Of course, my requirements are only useful insofar as our ethical and legal regulations give preferential treatment to humans over nonhumans. But there is reason to believe that the human/nonhuman distinction is not well supported. A number of philosophers—most famously, Peter Singer—have argued against the human/nonhuman distinction on the basis that it is merely biological and thus lacks normative force. (Just because someone is a member of the species *Homo sapiens* does not mean that we *ought* to give him or her preferential treatment—at least not without an additional argument). Opponents of the human/nonhuman distinction tend to instead favor the person/nonperson distinction (or some version of it) where a person is someone who has the characteristics that we believe to be morally relevant, e.g., the ability to feel pain, the ability to reason, etc. and insofar as one has these characteristics

one can be a person even if one is not human. Conversely, insofar as one lacks these characteristics, one can be a nonperson even though one is human.

Given this distinction, it may seem obvious that a proponent of the personhood view ought to find the humanness of part-humans irrelevant to how we ought to judge their moral status. However, I argue that this need not always be the case. The secondary aim of my dissertation, then, is to consider the moral status of part-human organisms from the person/nonperson distinction instead of the human/nonhuman distinction. What I show is that the causal history of a morally relevant characteristic—in this case, whether it came about as a result of a human transplant or a nonhuman transplant—can make a difference as to how we ought to judge the moral status of the recipient of that transplant.

Summary of Chapters

The idea of improving or prolonging life by replacing a failing body part with a healthy one has a long history. In Chapter 2, I offer a brief account of the history of xenotransplantation—the transplantation of living cells, tissues and organs from one species to another. The chapter begins with sheep blood transfusions of the 17th century, then moves through frog tissue grafts of the 19th century, and finally ends with ape testicle and organ transplantations of the 20th century.

In the 1970s, the techniques used to transplant parts across species changed dramatically. Scientists were still working on improving the transplantation of blood, tissues, and organs but the focus shifted to genes, chromosomes, nuclei and eventually stem cells. In Chapter 3, I present four modern day part-human candidates: 1) *chimeras*: made by transferring cells, tissues or organs; 2) *hybrids*: made by mixing gametes; 3) *cybrids*: made by transferring nuclei; and 4) *transgenics*: made by transferring genes. I explain how each part-human candidate is made and provide examples from current research.

In Chapter 4, I look at some of the ways in which philosophers have thought about parts and wholes to see if any of the available part/whole distinctions can help delimit animals partially composed of human parts from animals that are part-human. I begin with *mereology*, a metaphysical theory of the relations between parts and wholes. I then look at an applied form of mereology, *bio-ontology*, which is intended to capture the unique nature of parts and wholes in biology. From there, I turn to an *institution-based* approach to parts and wholes that has become the default strategy for delineating part-humans in bioethics. Finally, I end with two part/whole distinctions often used to help categorize biologically engineered animals: 1) the *quantitative* approach, by which the degree of humanness is calculated via the ratio of human to nonhuman parts; and 2) the *germ-line/soma distinction*, an approach that emphasizes placement instead of number of

human parts in the genetically engineered animal. After explaining the virtues of each approach, I argue that none of them can adequately delineate part-humans.

In Chapter 5, I provide an approach that involves establishing the minimum that is required for an animal to count as part-human. I argue that whether an animal is part-human or merely partially composed of human parts depends on the transposability of parts. A suitably transposable part is characterized by its giving rise to the same characteristic in both recipient and donor. Consider the following example as a demonstration of this point. In a recent experiment, human chromosome 21 was transferred into a mouse. The experimenters hoped that the transfer would create a nonhuman animal with Down syndrome. But whether the altered animal should be considered part-human or merely partially composed of human parts depends, to some extent, on whether or not human chromosome 21 can give rise to Down syndrome in mice. I argue that a part is transposable across species if the following three requirements are met: 1) the right partitioning frame is chosen; 2) part-boundaries are correctly identified; and 3) contextual constraints are eliminated. If the requirements are met, then the animal has part-human potential. Otherwise, it does not.

Up to this point in the dissertation, my emphasis will be on the importance of establishing the relative humanness of part-humans for the sake of ethical and legal regulations based on the human/nonhuman

distinction. But in the last chapter, I ask whether ethicists who oppose giving preferential treatment to humans over nonhumans—and instead favor some version of the person/nonperson distinction—ought to find the humanness of part-humans irrelevant to how we ought to judge their moral status. Although it may seem obvious that a proponent of the personhood view will find the causal history of an acquired characteristic—for example, whether it came about as a result of a dolphin or a human transplant—morally irrelevant, I argue that this need not be the case. Causal history is morally irrelevant to the *ontological* moral status of the animal, but *epistemically* relevant to our ability to detect an animal's moral status. I end with a summary of my dissertation.

CHAPTER 2

BRIEF HISTORY OF PART-HUMANS

The idea of improving or prolonging life by replacing a failing organ with a healthy one is at least 5,000 years old. Mythological stories about transplantation provide evidence that this concept has a long history. Probably the oldest accounts of transplantation come from Indian mythology. In Indian scriptures, various individuals are beheaded by the God Siva during his fits of anger. For example, Siva beheads Genesha but then agrees to bring him back to life (Kahan, 1989). When the head cannot be found, Siva asks his companions to bring back the head of the first living being they encounter that is misbehaving. The companions bring back the head of an elephant that was sleeping with his head facing north—an offence in the Hindu religion, because it causes the North Pole to disturb the peace of the universe. The elephant's head is then attached onto the beheaded trunk of Genesha bringing him back to life.

Stories about transplantation are also part of Chinese mythology. For example, there is an old tale about 'Judge Lu' who performed at least one

heart and one face transplant. First, he removed his friend's heart while the friend was asleep and replaced it with a better one. Afterwards, Judge Lu put his friend's heart on the table and told him that his heart was useless for composing essays because its holes were plugged. Afterwards, his friend's writing greatly improved. In fact, his friend was so pleased with the results that he asked Judge Lu to perform another transplant, "If you can exchange a heart, surely you can do the same for my wife's ugly face. I beg you to try your craft on her" (Bhandari & Tewari, 1997, p. 497). A few days later, Judge Lu returned with the head of a beautiful young woman and performed a successful face transplant.

Aside from mythology, the first actual transplantation experiments probably date back to 600 BC when Susrata, an Indian surgeon, used human skin flaps to replace human noses—noses were often cut off as punishment during that time (Deschamps, Roux, Sai, & Gouin, 2005). Early transplants were most likely unsuccessful, although they took place between members of the same species and they involved the transfer of cells and tissues (e.g., bone, skin, blood, etc.) rather than organs. Organ transplants came later because they are harder to perform—they require knowledge of how to control the bleeding after the sick organ is removed as well as knowledge of how to restore circulation once the healthy organ is in place (De Vito Dabbs, Dauber, & Hoffman, 2000).

Blood Xenotransfusions

Blood transfusions have been performed since ancient Rome, although before the 17th century blood was only transmitted by mouth. In ancient Rome, men who were seeking vigor would lap up the blood of fallen gladiators, and in the 15th century, Italian doctors prescribed sucking of blood from the arm veins of youth for rejuvenation (Maluf, 1954). The first intravenous transfusion was probably not performed until 1642 (see below). However, in 1615, Andreas Libavius, a physician and a chemist from Saxony, first described what an intravenous blood transfusion would entail:

> Given one has before oneself a strong, healthy, youth rich in spirited blood and a powerless, weak, cachectic old man scarcely capable of breathing. If now the physician wishes to practice the rejuvenating art on the latter, he should make silver tubes which fit into each other: open then the artery of the healthy person and introduce one of the tubes into it and fasten it to the artery; thereupon he opens also the artery of the ill person and fastens the other, female tube into it. These two tubes one fits into the other and notes herewith that the warm and spirited arterial blood of the healthy person flows into the ill person and imparts to him the fountain of life and drives away all faintness. (Maluf, 1954, p. 59-60)

Most likely, Libavius did not perform any blood transfusions himself. In fact, had he done so, he would probably find his assumption that blood would flow from the artery of the youth into that of the aged man (and not vice versa) to be problematic.

The earliest intravenous transfusion was performed in 1642 by Georg von Wahrendorff, a German horseman, who injected wine into the veins of his hunting dogs with the hope of treating an illness. He used a small fowl

bone for the task. Fourteen years later, in 1656, Christopher Wren at Oxford made a dog drunk by injecting wine and beer into its veins (Maluf, 1954). Experiments that involved injecting liqueurs into the veins of animals were considered noble at the time, in part, because they inspired new experiments. In the following decade, indirect blood transfusions of small quantities between dogs were performed, although Dr. Richard Lower was the first to perform a direct blood transfusion between dogs in 1665. In his *Tractatus de Corde* (1669), Lower describes one of his experiments in which most of the blood of a small dog is directly replaced by blood from two larger dogs:

> Having got ready the dogs and made other preparations as required, I selected one dog of medium size, opened its jugular vein, and drew off blood, until it was quite clear from its howls and struggles that its strength was nearly gone, and that convulsions were not far off. Then, to make up for the great loss from this dog by the blood of the second, I introduced blood from the cervical artery of a fairly large mastiff, which had been fastened alongside the first dog, until this latter animal by its restiveness showed in its turn that it was overfilled and burdened by the amount of inflowing blood. I ligatured the artery from which the blood was passing, and withdrew blood again from the receiving dog. This was repeated several times in succession, until there was no more blood or life left in two fairly large mastiffs (the blood of both having been taken by the smaller dog). In the meantime, blood had been repeatedly withdrawn from this smaller animal and injected into it in such amount as would equal, I imagine, the weight of its whole body, yet, once its jugular vein was sewn up and its binding shackles cast off, it promptly jumped down from the table, and, apparently oblivious of its hurts, soon began to fondle its master, and to roll on the grass to clean itself of blood. (Lower, 1969, in Maluf, 1954, p. 63)

Most of Lower's blood transfusions were between animals of the same species. However, Lower anticipated that human and nonhuman blood would mix just as well. Hence, in 1667, Lower and Edmund King transmitted sheep's blood into a 22-year-old Bachelor of Theology from Cambridge (Maluf, 1954). The purpose behind the transfusion was to change the man's character.

The function of blood was not known in the 17th century—oxygen was not yet discovered. Instead, people believed that blood determined a person's qualities. Not surprisingly, then, the point of Lower's blood transfusion experiments was to transfer the qualities of one individual into another, "'tis intended that these tryals shall be prosecuted to the utmost variety and subject will bear: As by exchanging the blood of Old and Young, Sick and Healthy, Hot and Cold, Fierce and Fearful, Tame and Wild Animals, and, that not only of the same but also of differing kinds" (Lower, 1666, p. 357). In particular, Lower chose to transmit the blood of a sheep into the 22-year-old man because the man's brain was considered "a little too warm" and the blood of a docile animal, e.g., a sheep, could cool it off. In the course of the experiment, a vein in the patient's arm was cut open and seven ounces of his blood were allowed to run out. Then the blood of the sheep ran into the man's vein. After about 2 minutes, the patient drew the pipe out of his vein saying that he has had enough. Once removed, sheep's blood ran through the pipe with full stream, indicating that the blood was in fact running from the sheep to the man for the duration of the experiment. The physicians who were

watching the experiment estimated that about 10 ounces of blood were received by the patient in that time. Six days later, the patient reported feeling much better (Maluf, 1954).

Around the same time, Jean-Baptiste Denis, a French philosopher, mathematician, and doctor of King Louis XIV, with the help of a surgeon named Paul Emmerez, performed a record number of four xenotransfusions to humans. The first one was to a young man with a fever, who was subject to "20 blood lettings" in an attempt to cure him.

Bloodletting, for the purpose of curing or preventing illness, was a common medical practice at the time. People believed that the proper balance of the four humours—blood, phlegm, black bile and yellow bile—was needed to maintain health. Thus, Denis's experiment, which involved adding blood to a patient rather than removing it, was very controversial. However, following a transfusion of 9 ounces of blood from a sheep, the patient reportedly leaped to his feet, full of energy, and in his excitement slaughtered his blood donor (Cooper & Lanza, 2000). Denis's second xenotransfusion was to a healthy man who got paid to volunteer. The third one was to a patient who was dying. The transfusion delayed death by only a few hours (Denis, 1667). By the time Denis performed his fourth transfusion, French physicians who were jealous of his work were starting to dislike him. However, his fourth patient would put an end to blood transfusions for over a century. Antoine Mauroy, a 34-year-old, newly-wed house servant, was considered to be mentally ill because

he would occasionally escape from his suburban home and spend time gallivanting in Paris. A gentleman who felt sorry for Mauroy's wife asked Denis for help. The thought was to diminish Mauroy's spirit through a blood transfusion from an animal of a gentler character, e.g., a calf. On December 19, 1667, Denis and Emmerez transmitted 6 ounces of blood from a calf into Mauroy's arm vein. The transfusion was performed in the presence of several physicians who reported that the patient seemed to improve and become quieter. A few days later, the procedure was repeated. This time, the patient had a reaction to the transfusion: irregular heartbeat, pain in his chest and kidneys, and a sensation of heat travelling up his arm while the blood was being transmitted. The day before Christmas, Mauroy's nose was bleeding and he had dark bloody urine. However, his wife insisted on a third transfusion after the patient again became maniacal.

There are conflicting reports as to whether or not the third transfusion actually took place (see, for example, Deschamps et al., 2005; Maluf, 1954; Tucker, 2011), but what is clear is that the patient died the following night. The physicians who disliked Denis bribed Mauroy's wife to state that the patient died during the transfusion. Denis was subsequently tried for manslaughter. In 1668, the Court exonerated Denis from any responsibility, concluding that the patient had been poisoned by his wife with arsenic. The Court also ruled that any future transfusions made to man must be authorized by a doctor from the Faculté de Médecine in Paris. In 1670, the

French Parliament declared transfusion to human beings illegal throughout France. The English Parliament and the Pope did the same shortly after. Although a few more transfusions were performed after that, the practice was set aside for the next 150 years. This was probably for the best, since ignorance of antisepsis and immunology would have resulted in serious complications. Today we know that sheep blood is rapidly destroyed by human antibodies and, consequently, sheep to human blood transfusions are often accompanied by "fever, chills, transient jaundice, discolored urine, and possibly more serious complications, such as acute kidney failure" (Cooper & Lanza, 2000, p. 28).

In 1816, a century and a half later, John Henry Leacock, a Scottish physician, performed eight blood transfusions between different animals and concluded that the donor and the recipient must be of the same species in order for the transfusion to be successful. Thus, he recommended interhuman transfusions (Schmidt & Leacock, 2002). Human blood types were yet to be discovered.

Tissue Xenografts

The first reported tissue xenograft was in 1501, by Muhammad Baha' al-Dawala, an Iranian surgeon who replaced a piece of a patient's skull with a bone from a dog, in order to treat his bacterial bone infection. The surgeon used a slice of cucumber to protect the brain (Rodriguez, 1995). Around the

middle of the next century, a similar procedure was performed by Job van Meekerent, a Dutchman. This time, the patient was a Russian nobleman who had lost part of his skull in battle. A bone from the skull of a dog was used to repair the damage (Haeseker, 1991). Although the xenotransplantation was successful, the nobleman had the dog bone removed at a later time when the Orthodox Church threatened him with excommunication. The Church claimed that no man could be saved if he had a dog bone in his head (Cooper & Lanza, 2000).

In Chicago in 1880, Dr. E. W. Lee applied a skin graft from a sheep to a burned 10-year-old girl. The surgeon used a pedicled graft, which is a graft where a portion of the skin from the donor site remains attached to the donor area while the remainder is attached to the recipient site. After a few weeks, new blood vessels will grow into the recipient site and the skin flap can be completely detached from the donor site. This technique is still used today, although only to move skin from one site to another on the same individual. Dr. Lee, however, used three pedicled skin flaps from a living lamb and applied them to the back of the burned girl. To prevent the skin flaps from tearing, the lamb was fastened to a wooden cage and its limbs were fixed still with plaster. However, the girl died attached to the lamb before any new blood vessels formed (Cooper & Lanza, 2000).

Unpedicled xenografts were also very popular in the late 1800s. Frogs were the preferred donor since they were easily obtainable and inexpensive.

Moreover, frogs do not grow fur or feathers, so they blend in better with human skin, and doctors discovered that even their pigment disappears a few days after transplantation. Thus, frog skin was used on ulcers and burns. In the British Indian Army, a surgeon performed between 300 and 400 frog xenografts, all of which were successful. Although it is unlikely that the grafts became a permanent part of the patients, they probably accelerated the healing process by protecting the ulcer or burn. In the 1960s and 1970s, pig skin was used explicitly for this purpose on patients with extensive burns (Cooper & Lanza, 2000).

Testicle Xenografts

Unlike skin and bone grafts, testicles were transplanted for the special purpose of revitalization and sexual rejuvenation. In 1889, Charles-Edouard Brown-Sequard, a French-American physician, injected himself with an extract of crushed dog and guinea pig testicles. He was 72 years old. The injections were said to have restored his strength and capacities (Schultheiss, Denil, & Jonas, 1997). Since then, a variety of drugs have been made from crushed animal organs, including thyroid extracts that are still used today for the palliative treatment of hypothyroidism (Deschamps et al., 2005).

Thirty years later, Serge Varonoff, a Russian emigrant, turned endocrinotherapy into a surgical procedure. His aim was to transplant the testicles of chimpanzees and baboons into men in order to rejuvenate them.

In 1920, Varonoff performed his first transplantation. The procedure was fairly simple: Varonoff would cut out the testicles from an anesthetized chimpanzee, slice each one into six sections and insert three sections per testicle into two recipients. In his book, *Rejuvenation by Grafting*, Voronoff reports doing 52 testicular grafting operations between the years 1920 and 1923. Most of the recipients were elderly men who had been sexually impotent for at least a decade. For example, a 74-year-old Englishman who, according to Voronoff, was hard to recognize 8 months after surgery, "The grafting had transformed a senile, impotent, pitiful old being into a vigorous man, in full possession of all his faculties" (Cooper & Lanza, 2000, p. 25).

However, the medical profession was highly skeptical of Voronoff's "Viagra" and according to Jean Real, a French documentary film director, Parisians did not take his work very seriously:

> Many satirical newspapers and cabarets mocked the grafted men. The Follies Bergère even created a show around the subject. The whole of society laughed and the grafting of monkey 'balls' became a national joke. An ashtray representing a monkey protecting his private parts and with the text 'Non Voronoff, tu ne m'auras pas!' (No Voronoff, you won't get me!) was found on many café tables. (Cooper & Lanza, 2000, p. 25)

The negative opinion of the press did not stop Voronoff. In fact, he started transplanting ape ovaries into women for the treatment of menopause and at some point he even tried the reverse: He transplanted a woman's ovary into a female chimpanzee and then tried to inseminate the chimpanzee with human sperm. The chimpanzee did not become pregnant, however.

In the course of his life, Voronoff transplanted ape tissue to 2,000 human patients (Deschamp et al., 2005). Without immunosuppressive drug therapy, which was not yet invented, it is unlikely that any of the transplanted tissue survived for more than a few days. The positive effects of the transplants were probably psychological. But to his credit, Voronoff had various medical visions that exceeded the science of his time. For example, he recognized the need to grow spare parts for the human body and he even set up a farm on the French Riviera to breed monkeys imported from Africa. Today, surgeons are considering setting up pig farms to grow organs for humans. Voronoff also had visions of human to human organ transplants. He predicted that:

> …in large towns in which fatal accidents are so frequent and so varied, patients waiting for organ transplantations would be sent to special hospitals to which any person dying from an accident would be transferred and, after thorough examination, his or her organs would be removed in order to be transplanted. (Cooper & Lanza, 2000, p. 26)

Voronoff's predictions were remarkably accurate, although he did not perform any human-to-human organ transplants in the course of his life. He came very close in 1928, when a criminal executed by guillotine had donated his body to science, but the authorities of Paris denied Voronoff permission to retrieve his organs (Cooper & Lanza, 2000).

Organ Xenotransplants

Two Frenchmen, Mathieu Jaboulay and his pupil Alexis Carrel, made organ transplantation possible by developing a technique for joining together blood vessels. In 1912, Carrel won the Nobel Prize in Physiology and Medicine for developing the technique (Cooper & Lanza, 2000). The kidney was the most popular organ transplanted at the time, because it is a paired organ with a single artery and its function and malfunction is readily visible in the production of urine (Deschamps et al., 2005). In 1906, Jaboulay transplanted the kidney of a pig killed 3 hours earlier to the bend of the elbow of a 48-year-old woman and then, later in the year, a goat kidney to the bend of the elbow of a 50-year-old woman. The blood vessel from the kidney was connected to the patient's arm, but the kidney remained external to the skin. (Transplanting a body part to a position other than its normal anatomical position is known as "heterotopic transplantation," in contrast to "orthotopic grafting" where the body part is transplanted to its normal anatomical position). Heterotopic transplants are still performed today. For example, the oocytes of women who will undergo chemotherapy for cancer treatment, and will most likely become infertile as a result, can be frozen and then transplanted once the treatment is complete. The transplantation can be orthotopic or heterotopic. If it is heterotopic, the graft can be easier to monitor, e.g., on the forearm, or its revascularization can be enhanced by a larger blood supply, e.g., in the kidney capsule. However, heterotopic oocyte

transplants must be fertilized in vitro (Oktay et al., 2004; see also Paris, Snow, Cox, & Shaw, 2004).

Jaboulay collected 1.5 L of urine from the woman with a pig kidney. He had similar success with the woman who underwent a heterotopic transplant of a goat kidney. However, the kidneys of both of the women had to be removed after a few days. Jaboulay blamed the failure of the transplant on blood clots, but rapid rejection would have produced the same result (Cooper & Lanza, 2000). Three more kidney xenotransplants were reported in the early 20th century. In 1909, Ernst Unger transplanted the kidneys of a macaque onto the thigh of a 21-year-old woman. The woman died 32 hours later. In 1913, Schonstadt transplanted a kidney from a Japanese monkey to the arm of a young girl. The girl died 60 hours later after producing a few drops of urine. And finally, in 1923, Harold Neuhof transplanted a lamb kidney to a man who died 9 days later. After that, most surgeons realized that xenotransplantation was doomed to early failure and experiments stopped for the next 40 years. During that time, human-to-human organ transplantation became popular again although there was a real shortage of suitable organ donors, since the concept of brain death had not yet been established as a way of distinguishing which individuals were acceptable donors.

In large part, the failures of early transplantation experiments were caused by immunological rejection. Not surprisingly then, the arrival of

immunosuppressive drugs in the 1960s and 1970s again sparked an interest in xenotransplantation. In 1963, Keith Reemtsma, a professor of surgery at Tulane University in Louisiana, performed the first organ xenotransplantation with the assistance of an immunosuppressant—albeit a primitive one by today's standards. The kidney came from a rhesus monkey, but the 43-year-old patient died of shock 63 days later. In the next year, Reemtsma performed 13 kidney transplants from chimpanzees to humans. The chimpanzees came from either 1) the military, where they were used in experiments relating to space flight or 2) the circus, where they were no longer fit to perform. Most of the patients lived from 9 to 60 days after the transplant, with the exception of a 23-year-old schoolteacher who lived for 9 months. In fact, the schoolteacher went back to work and led a normal life until she died suddenly from an electrolyte imbalance. Remarkably, the autopsy showed no signs of rejection. Nine months without rejection is still the longest survival record for the xenotransplantation of an organ into a human recipient (Reemtsma, McCracken, Schlegel, & Pearl, 1964).

That same year, a surgeon named Thomas Starzl, along with his colleagues at Denver, were hoping for similar success—this time with baboon kidneys. They transplanted baboon kidneys to six human patients. The baboon kidneys were rejected slightly more aggressively than their chimpanzee counterparts, most likely due to a greater evolutionary distance between donor and recipient (Cooper & Lanza, 2000). There were a few more

kidney xenotransplants in the 1960s, but none in the last 40 years. An additional reason why kidney xenotransplants stopped being performed was that large amounts of urine were excreted in the first few days after transplant. Occasionally, the amount would reach 50 liters and would lead to circulatory failure and death (Cooper & Lanza, 2000).

At the same time that kidney xenotransplants became popular again, heart and liver xenotransplants were also on the rise. In 1964, James Hardy at the University of Mississippi performed the first heart xenotransplant. Hardy gave the heart of a chimpanzee to a 68-year-old man who was dying from heart disease. The patient died within 2 hours of the operation, reportedly due to the small size of the heart of the donor—the chimpanzee weighed only 44 kg and the heart could not pump enough blood to keep alive a patient who weighed considerably more. There were also a few isolated liver xenotransplants in the late 1960s and early 1970s with Starzl and his colleagues in Denver performing the first one in 1966. In the next few years, the same team transplanted chimpanzee livers to three children: 1) a 28-month-old child who survived for 9 days, 2) a 7-month-old child who survived for 26 hours, and 3) a child who survived for 14 days (Starzl et al., 1974). After that, liver xenotransplants did not become popular again until the early 1990s.

In the late 1970s, the pharmaceutical company Sandoz brought new hope for xenotransplantation with a new wonder drug. Sandoz had a

tradition of encouraging its travelling employees to bring back plastic bags of soil samples from wherever they went. The soil was then analyzed for the presence of fungi that might be used for antibiotics. Soil samples from Norway and Wisconsin revealed a new fungus, *Tolypocladium inflatum.* Although the fungus did not have antibacterial potential, it turned out to be the most powerful immunosuppressant researchers had seen to date. After animal and human trials, the drug was finally approved in 1983 by the U.S. Food and Drug Administration for use in preventing immune rejection. Sandoz named the drug 'Cyclosporine' (Miller, 2005).

A year later, the most famous xenotransplantation experiment took place. "Baby Fae" was born prematurely with a heart defect so severe that only a transplant could save her (Bailey, 1985). Upon learning of Baby Fae's condition, Leonard Bailey, a surgeon of Loma Linda University, proposed transplanting a baboon heart into the newborn to keep her alive until a human heart donor would became available. Bailey had never transplanted a nonhuman organ into a human, but with human organ donors of that size being extremely rare, he believed this was the only option. Moreover, in a preliminary study, Bailey transplanted the hearts of newborn lambs into newborn goats and was able to obtain a mean survival time of 72 days (Bailey, Jang, Johnson, & Jolley, 1985). The results of the preliminary study—along with the fact that human and baboon hearts are comparable in size, that Fae was immunologically immature, and that cyclosporine was now on

the market—gave Bailey hope that the experiment would work (Deschamps et al., 2005). The only problem was that Baby Fae was of blood group O and the rules governing organ transplants are the same as those governing blood transfusions: The blood types of the donor and the recipient have to be the same. However, baboons do not have blood type O, only A, B, and AB. Thus, even though six available baboons were tested and the one that triggered the weakest immune reaction was chosen, it was nonetheless not a match for Fae. The baboon was blood type B (Cooper & Lanza, 2000).

Baby Fae was a global sensation. The whole world watched as she survived the operation. But hope died quickly as her kidneys started to fail and eventually her heart followed. It is not clear whether the blood type mismatch was the determining factor in Fae's death or the fact that cyclosporine was not a strong enough immunosuppressive drug to prevent graft rejection. Either way, Baby Fae died 20 days after surgery and the hope of xenotransplantation seemed to have died with her. Moreover, because of all the publicity surrounding Baby Fae, many ethical issues were brought to the forefront and animal rights activists protested in front of the hospital where Bailey performed the surgery (Miller, 2005).

Xenotransplantation had a brief comeback in the early 1990s when a new immunosuppressive agent, FK506, was marketed (Warty et al., 1988). In 1992, Starzl transplanted the liver of a baboon to a 35-year-old patient and in 1993 to a 62-year-old man. Although the option of a human liver transplant

existed at this time, Starzl thought that a baboon liver had a better chance of survival because the liver failure of both patients was caused by hepatitis B. Since there was some evidence that suggested that a baboon's liver is resistant to the virus, and since a new human liver was likely to also be attacked by the virus, Starzl thought the baboon liver would provide a better option (Cooper & Lanza, 2000). Unfortunately, neither patient lived long enough to prove this hypothesis correct. The first recipient survived for 70 days but died of overwhelming sepsis and the second one survived for 27 days, never regained consciousness, and died of failure of vital organs. Nonetheless, the reason why xenotransplantation was approved for both of these patients is because a baboon transplant had some advantage over a human one.

In sum, organ xenotransplantation has not been successful. No patient who received an organ xenotransplant lived longer than 70 days (with the exception of Reemtsma's schoolteacher who lived for 9 months) and most patients who received an organ from a species other than a nonhuman primate died within a day (Cooper & Lanza, 2000). In spite of these disappointing results, xenotransplantation is again on the rise—this time with the help of advancing biotechnology. In the next chapter, I will discuss current methods used to transplant body parts across species.

CHAPTER 3

MAKING PART-HUMANS

In the 1970s, the techniques used to transplant parts across species changed dramatically. Although scientists were still working on improving the transplantation of blood, tissues and organs, the main focus shifted to genes, chromosomes, nuclei and eventually stem cells. Before I move to an explanation of how modern part-humans are made, let me first explain why scientists are interested in making such creatures. In the first place, scientists use part-humans to produce human characteristics in nonhuman animals. Since laboratory animals cannot fully replicate human physiology, scientists use part-human animals to investigate human specific biological processes and diseases without having to experiment on human subjects. Second, part-human research is used to create human cells, tissues and organs for xenotransplantation. This process often involves transferring human stem cells to a developing nonhuman fetus and harvesting the resulting organ from the mature animal for transplantation into a human. Third, part-human research is used to "pharm" animals as biological factories

for human products. For example, sheep have been genetically engineered to produce human insulin in their milk. The insulin is then harvested by pharmaceutical companies for the treatment of diabetes.

With that out of the way, the remainder of the chapter will be devoted to explaining how part-humans are made. In what follows, I focus on four part-human candidates: chimeras, hybrids, cybrids, and transgenics. My taxonomy of part-human candidates is based on how each one is made: 1) chimeras are made by transferring cells, tissues or organs between animals 2) hybrids are made by mixing gametes of different species 3) cybrids are made by transferring nuclei into enucleated eggs and 4) transgenics are made by transferring genes between animals. For alternative taxonomies see Bonnicksen (2009), Greely (2003), Robert (2006) and Taupitz & Weschka (2009).

Chimeras: Made by Transferring Cells, Tissues or Organs

Chimeras contain cell populations derived from at least two different zygotes of the same or different species (Taupitz & Weschka, 2009). In contrast, mosaics contain two distinct types of cells originating from a single zygote. Mosaicism typically arises during the course of development. For example, in early human female embryogenesis, one of the two X chromosomes will be functionally inactivated. As a result, in roughly half of the cells of a typical human female the paternal X chromosome is inactive,

while in the other half, the maternal X chromosome is inactive (Taupitz & Weschka, 2009). Since these distinct cell populations originate from a single zygote, human females are mosaics, not chimeras.

In contrast, some pregnant women exchange placental blood with their fetus. The blood cells from the child can persist in the mother for decades after the child is born (Bianchi, Zickwolf, Weil, Sylvester, & DeMaria, 1996). Here, the woman is a chimera because she contains cell populations from two different zygotes. In fact, later-born children can be chimeras as well, if the cells of elder siblings slip across the placental membrane during the mother's pregnancy.

There are different ways to create interspecies chimeras. Scientists can engraft fetal or adult tissues from one species to another, as long as there is some method available to prevent rejection of the graft. For example, the development of immunodeficient mice has made it possible to engraft human tissue onto mice without rejection. The first mouse of this kind—the Nude mouse—arose from a spontaneous genetic mutation. The mutation causes both hairlessness and an inability to generate mature T cells due to an impaired thymus—T and B cells of the immune system fight off foreign cells and infections (Shultz, Ishikawa, & Greiner, 2007). The severe combined immunodeficiency mouse (SCID) also arose from a spontaneous genetic mutation. The SCID mouse lacks both mature T and B cells and has since been manipulated to also mimic the human immune system. Human fetal

liver hematopoetic cells, fetal thymus and fetal lymph nodes have been transplanted into SCID mice to create SCID-hu mice that are immunologically humanized (McCune et al., 1988). These mice can support engrafted human T and B cells.

Various human tissues and organs have been engrafted and transplanted into immunodeficient mice, turning them into human-nonhuman chimeras. For example, scientists have been engrafting human tumors under the skin of nude mice for decades. Nude mice will not reject the tumor and the blood supply will enable the tumor to grow. "The mouse essentially becomes a cancer patient whose tumor can then be manipulated in various ways to understand cancer mechanisms and to test therapeutic protocols for human cancer" (Behringer, 2007, pp. 259-260). Other human tissues that have been successfully transplanted into immunodeficient mice include skin for the study of psoriasis (Boehncke, 1999; Raychaudhuri, Dutt, Raychaudhuri, Sanyal, & Farber, 2001), vaginal tissue for the study of HIV transmission (Kish, Budgeon, Welsh, & Howett, 2001), and hair follicles to test regenerative potential after transplantation (Hashimoto et al., 2001). Human tissues have also been transplanted into immunodeficient mice for the study of pathogens. The reason for this is that some pathogens will only infect humans (or nonhuman primates), while others that infect humans along with other animals may give rise to different symptoms in nonhuman animals as compared to humans. As a result, it is best to study pathogens in humanized

animals. Finally, donated human fetal organs have been engrafted into immunodeficient mice, albeit heterotopically, i.e., to a position other than their normal anatomical position (see Chapter 2). The cells of these heterotropically transplanted organs have been shown to grow and differentiate (Savidge et al., 1995; Thomas, Wang, & Hornsby, 2002).

Another method of creating chimeras is by organ transplantation. When a person's organ starts to fail, human-to-human organ transplants are not always an option because of the short supply of human organ donors. Consider, for example, that between the years 2001 and 2004, approximately 86,700 people per year were on the waiting for an organ transplant in the United States. In that time, approximately 25,400 organ transplants were performed annually and 6,700 patients died each year while waiting for a transplant (Hagen & Gitten, 2008). Due to the high demand for organ transplants, there has been a renewed interest in xenotransplantation. While having a pig heart replacement would obviously make one a chimera—since the population of cells that make up the organ originated from a different zygote—there is another sense in which the recipient would be a chimera: donor cells have been detected in the blood of recipients after a liver, kidney, heart and lung transplants (Taupitz & Weschka, 2009).

Scientists have been looking into pigs as a source of organs for a number of reasons. Pigs share some anatomical and physiological similarities with humans, e.g., pig and human organs are similar in size. Pigs also have a

short reproductive cycle and they give birth to multiple offspring at a time. Unfortunately, pig organs are prone to rejection. Although hyperacute rejection does not occur with small tissues or single cells, it occurs within minutes when vascularised organs are transplanted across species (Taupitz & Weschka, 2009). One way to minimize hyperacute rejection is to use immunosuppressive drugs. Another way is to outwit human immune defenses by genetically engineering a pig so that it will "appear" less like a foreign invader to the human immune system. The first transgenic pig, developed specifically for xenotransplantation, was born in 1992. The gene for an enzyme that builds sugars in porcine cell membranes was inactivated in this pig since human antibodies react to antigens, such as sugars, found on the surface of porcine organs (Renneberg & Demain, 2007). The idea was that the inactivation of this gene would help prevent rejection. Human trials of transgenic pig organ transplants are yet to be conducted.

Another way to prevent rejection of nonhuman organs is to "humanize" the organs at the cellular level. For example, Esmail Zanjani, a researcher at the University of Nevada at Reno, has injected human hematopoietic stem cells (i.e., blood stem cells) into sheep fetuses (Almeida-Porada, Porada, Chamberlain, Torabi, & Zanjani, 2004). According to Zanjani, the results were sheep with organs composed of 15% human cells, although some livers were as much as 40% human and contained structural units typical of human livers pumping human proteins (Shreeve, 2005). In the future, Zanjani wants

to figure out a way to purify multipotent cells from a patient's organ and inject them into sheep embryos, the idea being that the cells would contribute to half of the organs and when the organs would be transplanted into the patient, the sheep cells comprising the organ would be rejected, while the human cells would be accepted as a perfect match (Scott, 2006).

The benefit of using sheep rather than pigs is that it eliminates the risk of zoonosis—the transmission of infectious diseases from pigs to humans. For example, the porcine endogenous retrovirus (PERV) could, in theory, be passed on to humans through a transplanted organ. This poses an especially high risk for patients whose immune systems are suppressed to prevent rejection of the organ (Taupitz & Weschka, 2009). While PERV is not normally infectious to people, a recent experiment has shown that the transmission of the virus might be possible if human and pig cells fuse. In a recent experiment, after hematopoietic stem cells were injected into fetal pigs, human cells were found in their internal organs and blood system. What was more interesting, and what has never been observed before, was that over 60% of the nonpig cells were pig-human cell fusions (Ogle et al., 2004). Further tests showed that fused cells, unlike pig cells, are capable of transmitting the virus to uninfected human cells. This finding might help explain how diseases such as AIDS and SARS, which originated in nonhuman animals, were eventually transmitted to humans.

Besides being used to replace failed human organs, xenografts have also been used to treat neurological disorders. Fink et al. transplanted porcine fetal neurons into the brains of adult patients suffering from Parkinson's and Huntington's disease (Fink et al., 2000). In the past, neuronal replacement using human fetal neurons has been shown to be efficacious in patients with Parkinson's disease, but the use of human fetal tissue is limited for ethical reasons. Pigs were proposed as an alternative resource because of similarities in brain size. In the Fink et al. study, between 12 and 24 million porcine neurons were transplanted into the brains of 24 patients. The neurons were obtained between embryonic days 25-28 for Parkinson's patients and between days 35-38 for Huntington's patients. The gestation period for pigs is around 114 days. Although no deleterious side effects were observed in either patient group, no functional improvements were achieved in Huntington's patients and only a slight clinical improvement was achieved in Parkinson's patients (Taupitz & Weschka, 2009).

Thus far I have only talked about the creation of chimeras where either the donor or the recipient is at least as old as a fetus. But chimeras can also be made from two eight-cell embryos pushed together in a culture dish. The two cell populations can sometimes grow into a single blastocyst and occasionally even develop to term (Behringer, 2007). For example, in 1987, a "geep" was created from the fusion of early stage goat and sheep embryos

(Fehilly, Willadsen, & Tucker, 1984). The geep looked like a chimera because its fur was patchy—some parts were hairy like a goat's and some parts were woolly. The creator of the geep also noted that:

> The animal behaved like a goat, but did not quite smell like one, and preferred the company of sheep. Its sheep cells were male but the sex of its goat cells was not known. It proved fertile in many matings with ewes [female sheep] but has not, so far, with does [female goats]. (Silver, 2006, p. 181)

The fact that the geep had characteristics of both goats and sheep is among the reasons people are uneasy about creating human-nonhuman chimeras by pushing early embryos together. However, scientists have attempted to make human-nonhuman chimeras by injecting human embryonic stem cells (ES cells) into more advanced nonhuman embryos.

Such experiments only became possible after the first human ES cell lines were derived from human blastocysts in 1998 (Thompson et al., 1998). ES cells have the capacity to form all cell types—they are totipotent. The totipotency of ES cells diminishes as they start to differentiate but they can still contribute to all tissues of the embryo, including the germ cells, even several days after fertilization. Their differentiation proceeds as follows. At the early cleavage stage, when the embryo divides into a number of smaller cells without increasing in overall mass, ES cells form two groups—the trophectoderm and the inner cell mass (Wolpert, 2002, p. 43). The embryo is now a blastocyst. The cells of the blastocyst are minimally committed with respect to their developmental potential. The trophectoderm cells will form

extra embryonic structures, e.g., the placenta, and the inner cell mass cells will give rise to the embryo proper. Next, the cells move extensively and differentiate again into one of three types of cells, each forming a distinct layer of the embryo, the ectoderm on the outside, and the mesoderm and endoderm layers on the inside. In mammals, these cells will give rise to more than 200 different cell types, e.g., blood, muscle, cartilage, nerve, etc. Their differentiation is a gradual process that occurs over successive cell generations. For example, ES cells that have differentiated into neural stem cells are still multipotent because they have the capacity to generate different cells of the nervous system, i.e., neurons, astrocytes, and oligodendrocytes, but each generation becomes progressively more differentiated (Wolpert, 2002). For the purposes of making a chimera, the cells to be injected, and the cells of the recipient embryo, can be at different developmental stages. For example, differentiated human neurons can be injected into the brain region of an advanced embryo. However, the less differentiated the donor cells the more likely they are to contribute to all cell types of the recipient organism.

Examples of experiments that used human stem cells to make interspecies chimeras include human-mouse chimeras (James, Noggle, Swigut, & Brivanlou, 2006), human-chicken chimeras (Goldstein, Drukker, Reubinoff, & Benvenisty, 2002), human-rat chimeras (Yokoo et al., 2005), human-sheep chimeras (Almeida-Porada et al., 2004), human-pig chimeras (Fujiki et al., 2003), and human-goat chimeras (Zeng et al., 2006). (For additional examples

see Taupitz & Weschka, 2009). However, one of the most controversial experiments involved engrafting human neural stem cells into the brains of old world monkey embryos (Ourednik et al., 2001). Since old world monkeys are closely related to humans, there were few anatomical and physiological barriers in place that could prevent the human neurons from contributing to the brains of the chimeras—the kind of barriers that would be in place if the cells were injected into mouse brains, for example (see Chapter 5).

Hybrids: Made by Mixing Gametes

A hybrid is made by mixing gametes, i.e., sperm and egg, of two different species (Taupitz & Weschka, 2009, p. 28). The most well known example of a hybrid is the mule, generated by the breeding of a male horse with a female donkey. Conversely, a hinny is generated by the breeding of a female horse with a male donkey. Mules and hinnies have been bred and used for carrying heavy loads for the last 5,000 years. Normally, they are infertile but occasionally offspring from mules mated with horses and donkeys have been reported (Rong et al., 1988). Other hybrids, generated by either natural mating or artificial insemination, include the liger (a hybrid from a lion and a tiger), the zeedonk (a hybrid from a zebra and a donkey), and the coywolf (a hybrid from a coyote and a wolf). More recently, a hybrid from the natural mating of a sheep and a goat was also documented (not to be

confused with the "geep," which is a chimeras rather than a hybrid) (Letshwenyo & Kedikilwe, 2000).

At the beginning of the 20th century, there was an interest in doing experimental research on the "Descent of Man" by breeding man and apes (Taupitz & Weschka, 2009). Among the interested parties was Ilya Ivanov, one of the pioneers of artificial insemination. Ivanov, along with his Russian team, set out to Africa to inseminate female orangutans with human sperm. However, a pregnancy was never obtained (Rossiianov, 2002). Since then, no human-nonhuman hybrid was ever created, although, to this day, human-nonhuman fertilized eggs continue to be produced through the "hamster test."

The hamster test has been used to test the fertilization capacity of human sperm since the 1970s (Yanagimachi, Yanagimachi, & Rogers, 1976). Using eggs to test the viability of sperm is supposed to reduce costly IVF-cycles, especially if the sperm is not viable, and the use of hamster eggs is supposed to reduce the wasting of human eggs. To conduct a hamster test, fresh human semen is collected from an adult male donor. After induced ovulation, the hamsters (*Mesocricetus auratus*) are sacrificed and their eggs are collected from their oviducts. Insemination of the hamster eggs with human sperm is performed *in vitro* and incubation is carried out for 3 hours. The samples are then placed on microscopic slides to observe if the sperm were able to penetrate the egg. Following the assessment, the samples are either fixed and stained or discarded. Although the fertilized eggs are not

allowed to proceed further, it is very unlikely that the fertilized eggs would lead to viable embryos given the evolutionary distance between humans and hamsters (Taupitz & Weschka, 2009).

Cybrids: Made by Transferring Nuclei

A cytoplasmic hybrid, or a cybrid, is created by inserting a nucleus of a somatic cell into an egg cell whose nucleus has been removed. The nucleus comes from one species and the enucleated egg comes from another. The technique used to make cybrids is the same technique that was used to create Dolly the sheep, although Dolly was not a cybrid because both the nucleus and the enucleated egg used to make Dolly came from the same species. The technique proceeds as follows. First, the somatic cell—whose nucleus is to be transferred into an enucleated egg—needs to return to its totipotent stage. All cells start out as totipotent cells but as they differentiate many of their genes become inactivated and they lose their ability to become any cell in the body. In fact, out of the 25,000 genes in the human genome, only 2,000 are active in any somatic cell (Houdebine, 2008). The rest of the genes are inactive. For example, a nerve cell does not need to produce insulin so the genes involved in the production of insulin will be inactivated in a nerve cell. However, those same genes will be active in an islet cell. In order to create a cybrid, or to clone a sheep like Dolly, all the genes of the somatic cell need to be reactivated. This can be done by starving the somatic cell in a broth poor

in nutrients (Renneberg & Demain, 2007). However, the genome of the somatic cell might have accumulated some damage in the course of the individual's life, e.g., damage from UV radiation, X-rays, reactive oxygen radicals and toxins. Normally, we would not be aware of such damage, as long as it occurred in the part of the genome that is inactive in a given cell, but the damage can show up once the genes are reactivated. This might explain why Dolly aged prematurely.

Once the somatic cell is obtained and starved in a low-nutrient broth, the nucleus is removed and inserted into an enucleated egg with a micropipette. The egg now contains a nucleus from one species (with the same number of chromosomes as it would if sperm and egg had met) and the cytoplasm and mitochondrial DNA from another species. Next, electric impulses are used to stimulate cell division. Dolly proved that if the donor nucleus and the enucleated egg come from the same species, the embryo can develop to term if implanted into a surrogate mother. However, this is no easy task. Out of the 277 attempts, Dolly was the only success. Nonetheless, the result overturned an enduring dogma in biology, that development only runs in one direction. Once Dolly was born, it was no longer true that all the cells in the body, e.g., brain, muscle, bone, skin, etc., must be derived from a fertilized egg and not the other way around. Dolly proved that "a normal somatic cell can "forget" all of its specifications, behaving like a totipotent fertilized egg cell" (Renneberg & Demain, 2007, p. 251).

There are two main reasons for creating cybrids. The first is to generate embryonic stem cells for use in medical research. The cells could be transplanted into a patient without the worry of rejection, since the nuclear DNA would be the same as the patient's. Ideally, the researchers would want to use a human egg for this purpose but there is a shortage of them. An IVF clinic struggles to collect 10 to 20 donated eggs in a week. In contrast, 200 cow eggs can be obtained from a single slaughterhouse in a day. For example, Chen et al. used rabbit eggs, instead of cow eggs, to generate human-rabbit cybrids (Chen et al., 2003). Nuclei were removed from male foreskin and female facial skin and injected into enucleated rabbit eggs. The embryos were allowed to develop to the blastocyst stage, although it is not clear whether an attempt was made to allow the cybrid embryos to develop past that stage. The ES cells exhibited most of the properties of conventional human ES cells, they tested positive for pluripotency, and they successfully differentiated into mature neurons (Taupitz & Weschka, 2009).

The second reason for creating cybrids is to preserve endangered species by transplanting the nuclei of an endangered species into the enucleated eggs of a well populated species (Loi, Galli, & Ptak, 2007). For example, in China scientists successfully transferred the somatic cell nuclei of giant pandas into rabbit eggs. The panda-rabbit cybrid embryos developed up to the blastocyst stage. After that, 2,300 of them were transferred into 100 rabbit recipients, but none of the rabbits became pregnant. However, new

evidence shows that the panda-rabbit cybrid embryos can implant in the uteri of a third species—the domestic cat (Taupitz & Weschka, 2009).

Cybrids, as well as clones like Dolly, are expected to be identical in phenotype to their nuclear donor. For example, the first cloned cat was named Carbon copy, Cc for short, with this expectation in mind. However, Cc's coat pattern was not identical to that of its nuclear donor. Why? Because nuclear DNA is not the only contributor to an animal's characteristics. There are environmental factors, e.g., the position of the embryo in the uterus has an influence on which hair follicles are reached by the pigment producing cells (Renneberg & Demain, 2007), and mitochondrial DNA, which does not come from the nuclear donor, also contributes to the phenotype. Mitochondria contain DNA that is independent from the DNA in the nucleus, so when the egg cell is enucleated the mitochondria remain. The number of mitochondria in each cell varies as the energy needs of a cell fluctuate. If the energy need is high, mitochondria will grow and divide. Hence, mitochondria can make up as much as 25% of the cytoplasm. Its primary function is transforming glucose into energy, but mitochondria are also involved in cell death, steroid synthesis, and other cell-type specific functions (Taupitz & Weschka, 2009). Moreover, some experiments have shown that either the mitochondria or something else in the cytoplasm contributes to vertebral development in fish. When the nucleus from a carp cell was introduced into an enucleated goldfish egg, some aspects of development mimicked the goldfish rather than the

nuclear donor (Taupitz & Weschka, 2009). In particular, the vertebral number of the cybrid was typical of a goldfish—26 to 28—rather than of a carp—33 to 36—showing that the enucleated egg of the goldfish can have an evident impact on certain developmental characteristics.

Transgenics: Made by Transferring Genes

A transgenic animal is created by splicing sequences of foreign DNA (called transgenes) into its genome in order to introduce or delete specific characteristics. The exogenous DNA is introduced early in development so that it can be transmitted through the germline. Although there are various methods used to make transgenic animals, they all begin with gene cloning, i.e., making numerous copies of the DNA sequence that will become the transgene (Nicholl, 2002). The point of gene cloning is to isolate the DNA sequence and make enough copies of it for multiple experiments. Standard methods of gene cloning either amplify DNA *in vitro* or *in vivo*. A popular *in vitro* method of amplifying DNA is the polymerase chain reaction (PCR) while a popular *in vivo* method relies on the help of microorganisms such as bacteria (Gilbert, 2000). However, the problem with using bacteria is that their primary transcript (DNA) does not undergo post-transcriptional modification. In humans, when RNA molecules are copied from DNA molecules, as part of the process of protein synthesis, some parts of the DNA, i.e., introns, are processed out of the primary transcript and are thereby not

copied. Since bacteria lack the means to remove introns, the gene for human insulin needs to be inserted into the bacterium intron-free.

Luckily, a complementary, intron-free copy of the desired DNA sequence can be made from RNA using an enzyme called "reverse transcriptase." The reverse transcriptase enzyme comes from retroviruses. The genetic material of retroviruses is composed of RNA rather than DNA but it is converted into DNA, via reverse transcriptase, so that the virus can blend in with the genetic material of the invaded cell and be copied during each cell division (Sanderson, 2007). Now, human cells contain RNA molecules that correspond to the DNA sequences of the genes being expressed in any particular cell. Thus, while the gene for human insulin is found in every cell of the body (insofar as almost all of the cells of the human body contain the same DNA) its complementary RNA can only be found in the pancreatic cells where the gene is expressed. If we purify the RNA sequences out of the pancreatic cells, then using reverse transcriptase we can make the complementary, intron-free DNA copy, ready to be inserted into bacteria.

A gene can be inserted into a bacterium via a plasmid, i.e., a small circle of DNA. The genetic material of bacteria is contained in several plasmids as well as one chromosome. However, the DNA contained in the plasmids is not essential for cell growth and division. Given that plasmids are used by a bacterium, but not essential to its function, means that plasmids can be isolated, transformed, reinserted and the bacterium will still accept

them as part of itself (Hill, 2002). Every 20 minutes, when the bacterium divides, the plasmid, along with the transgene, will be duplicated. Of course, the transgene must first be inserted into the plasmid. This task is at the heart of recombinant DNA technology since it consists of taking a strand of DNA and *recombining* it into another string of DNA. Restriction endonucleases enzymes, also known as restriction enzymes, are essential for this task. They are found in bacteria where they are used as a defense mechanism against viral infections. The enzymes cut invading DNA (assuming the DNA is viral) at very specific sites given a specific sequence. For example, the first restriction enzyme discovered (out of the ~900 isolated to date) was EcoRI found in *Escherichia coli* (Hill, 2002, p. 92). EcoRI looks for the following double-stranded sequence:

5' GAATTC 3'
3' CTTAAG 5'

Once the sequence is identified, the enzyme cuts each strand between the letters G and the closest A:

G AATTC
CTTAA G

Next, the DNA fragments separate from each other and the protruding 3' and 5' ends, known as "sticky ends," will bond with complementary sequences. The origin of the sequences does not affect their ability to bond together. In fact, if two different DNA sequences are cut with the EcoRI enzyme and mixed together, the unpaired 5' AATTC 3' sequence will bind with the

unpaired 3' TTAAG 5' sequence. What helps them "stick" is an enzyme called ligase (Sanderson, 2007). Ligase helps repair broken bonds when they occur in a cell as a consequence of DNA replication. It is a kind of molecular glue. Once the transgene is glued into place, the plasmid can re-enter the bacterium via its pores, e.g., the pores of some bacteria open when placed in a medium of calcium sulfate.

The final step of gene cloning involves screening for bacteria that actually took up the plasmid and thereby contain the transgene. Screening is typically done by applying some pressure that will allow bacteria with the insert to survive above the others. For example, the pressure may be in the form of antibiotics (Nicholl, 2002). If the plasmid with the insert contains genes for ampicillin resistance, then only the bacteria with the plasmid will survive and grow in an ampicillin medium.

As elaborate as the process of gene cloning may seem, it is only the first step of making a transgenic animal. Next, the cloned gene needs to be inserted at a very early stage of development, ideally the single-cell zygote stage, so that all of the cells of the organism (including the germ cells) can receive the transgene. One way to do this is with the help of a vector, e.g., a defective retrovirus. The first transgenic animals were successfully created by infecting mouse embryos with retroviruses. The retrovirus is defective insofar as it does not produce infectious viruses but it will nonetheless

incorporate the trasngene into the genome at one of the provirus integration sites.

While the retrovirus method can be used successfully to make transgenics, it has two limitations. First, it has size limitations—only 8 kilobases of foreign DNA can be transferred via a retrovirus—and second, the number of provirus integration sites in the genome can vary from one animal to the next—from one integration site to more than 20 (Taupitz & Weschka, 2009). Of course, depending on the goal of the experiment, these limitations may not be an obstacle. For example, the retrovirus method was used to make fluorescent piglets in Munich. The green fluorescent protein (GFP), which converts UV light into low-energy green light, was first isolated from the jellyfish *Aequorea Victoria*. When coupled with a protein, GFP can make the journey of the protein through a cell visible. GFP can also be used to monitor levels of stress in animals. Researchers in Singapore are trying to engineer a zebrafish from the Ganges, a highly polluted river in India, in such a way that the fish would glow green when under stress, due to heavy metals in the water (Renneberg & Demain, 2007).

Pronuclear injection is another method that can be used to make transgenic animals. When sperm and egg unite to produce a zygote, foreign DNA can be directly injected into either the male or the female pronucleus via a micropipette—no vector is needed. The problem with this method is that the insertion of the transgene occurs at random. Consequently, it is

necessary to generate more than one line of animals with each transgene to identify a similar change in phenotype that could be attributed to the transgene and not to some other factor. In contrast, the ES cell method allows for the integration of the transgene into specified locations in the genome. Here, ES cells are first isolated from the inner cell mass of the blastocyst and then segments of the genome can be replaced with foreign DNA fragments using a technique called "homologous recombination" (Capecchi, 2005). The cells are then injected back into the inner cell mass of a blastocyst but the offspring will be chimeras, since only a portion of the cells carry the transgene. However, subsequent crossbreeding will result in homozygous transgenic lines (Renneberg & Demain, 2007). Hence, this method has some advantages over the other two methods, i.e., large amounts of DNA can be transferred and one can control the site of insertion. Its major drawback, however, is that for reasons yet unknown, it only works on mice (Taupitz & Weschka, 2009).

Regardless of which method is used, another problem to worry about is possible toxic effects of the transgene product. If the transgene is expressed incorrectly, the effects could be lethal. To avoid this problem, the inserted sequence has to include both a coding region—the sequence that ultimately codes for a protein, e.g., insulin, and a control region—the sequence that regulates the expression of the gene, e.g., a promoter to which RNA will bind to initiate transcription. Some promoters drive a high level of constant

transcription in most cell types and developmental stages. Others provide more control over patters of expression. A gene fused with a tissue specific promoter, for example, will only produce its protein product in the tissues specified by that promoter. In addition, it is possible to generate a transgenic animal with a silent transgene that can become activated at any time by the application of certain drugs (Taupitz & Weschka, 2009). Once the transgene, plus the appropriate control region, are inserted, the embryo is transferred to the uterus of a pseudopregnant female. In some species, females can become pseudopregnant following an estrus in which they engage in coitus with infertile males. Afterward, the females may develop mammary glands, lactate and build nests. If the pseudopregnant females carry the embryo to term, the pups will be transgenic.

One reason to create interspecies transgenics is to model human diseases in nonhuman animals to ultimately develop treatments. Another reason is to create "pharm" animals—interspecies transgenics that can secrete human proteins in their body fluids. Pharmaceutical companies then collect the proteins and distribute them to people in the form of drugs. Human proteins can be expressed in a variety of biological fluids, e.g., milk, urine, saliva, and seminal fluid. Milk is the preferred fluid, because of its large scale volume production, but urine has some advantages, too. It can be expressed in both sexes, harvested soon after birth and expressed throughout the life of an animal. However, in spite of these advantages, collecting

proteins from urine is also time and cost consuming, at least more so than collecting proteins from milk (Melo, Canavessi, Franco, & Rumpf, 2007).

In the late 1980s, GenePharming, a Dutch company, set out to create transgenic cows that could secrete the human protein "lactoferrin" in their milk. Lactoferrin is a protein found in breast milk that improves the absorption of iron and protects against intestinal infections. Out of the 2,400 transgenic embryos that were created, only 128 developed far enough to be transplanted into cows, and only one was born. Unfortunately, however, the calf was a male and thus unable to produce milk containing the protein. A few years later, its transgenic sperm was used to fertilize nontransgenic cows and, eventually, eight transgenic female calves were born. Three of them died and the rest were fertilized with nontransgenic sperm once they became sexually active. After they gave birth they began to produce milk. The milk contained human lactoferrin in concentrations between 0.3 to 2.8 grams per liter and was identical to the lactoferrin found in human breast milk (Renneberg & Demain, 2007).

To offset some of the costs of a mammalian farm, low cost rodent farms have also been used. Mouse milking machines can milk a mouse and produce 4 milliliters of milk per day. For example, since the late 1980s, transgenic mice have been producing t-PA, an agent that dissolves blood clots in heart attacks. Transgenic chickens, on the other hand, have been engineered to produce antibodies in their eggs. The egg white contains 3 to 4 grams of

protein and chickens lay an average of 250 eggs per day (Renneberg & Demain, 2007). Finally, goats, which reproduce faster than cattle, have been engineered to produce spider silk proteins in their milk. Spider silk is as strong as steel but at the same time light and elastic. These properties are ideal for making artificial ligaments and tendons or for creating bulletproof vests. Mass producing spider silk by keeping large numbers of spiders in the laboratory is not an option because spiders are territorial. They kill each other if they live close together. Hence, scientists created transgenic goats capable of secreting spider silk protein in their milk as a solution to this problem. However, when the fibers were obtained, they did not meet the tenacity and resistance properties present in spider silk, most likely because of a faulty purification process that is critical for obtaining the desired product (Melo et al., 2007).

Summary

In closing, let me briefly review the four part-human candidates I introduced in this chapter: chimeras, hybrids, cybrids and transgenics. Chimeras contain cell populations derived from at least two different zygotes of the same or different species. Currently, there are a few different ways to create human-nonhuman chimeras. First, human tissues and organs can be engrafted onto immunodeficient nonhuman animals—e.g., human tumors in Nude mice. Second, nonhuman organs can be transplanted into humans.

However, as we learned in the last chapter, nonhuman organs tend to be rejected by humans—with or without immunosuppressant drugs—hence, it is best to "humanize" the nonhuman donor before transplantation to prevent rejection—e.g., sheep chimeras whose organs are composed of cells of human origin. Last, nonhuman cells can be engrafted onto humans—e.g., porcine neuron in the brains of Parkinson's patients—and conversely, human cells can be engrafted onto nonhuman animals—e.g., human neurons in the brains of old world monkey embryos.

Hybrids are made by mixing gametes, i.e., sperm and egg, of two different species. No human-nonhuman hybrid was ever created but human-nonhuman fertilized eggs have been, and they continue to be created to test the fertilization capacity of human sperm, known as the "hamster test." Yet another part-human candidate is the cytoplasmic hybrid, or cybrid, made by inserting a nucleus of a somatic cell of one species into an enucleated egg of another species. An enucleated egg lacks a nucleus but contains its own cytoplasm and mitochondrial DNA. Scientists have attempted to make human-nonhuman cybrids by injecting human nuclei into enucleated rabbit cells, but the cybrid embryos did not develop past the blastocyst stage. Finally, transgenics are made by splicing sequences of foreign DNA into the recipient's genome. Human-nonhuman transgenics are usually created for medical purposes, e.g., to secrete human proteins in their body fluids or to mimic human diseases.

CHAPTER 4

PART/WHOLE DISTINCTIONS

What is the relation between a whole and its parts? Is a whole identical to its parts? Is a whole greater than the sum of its parts? Can a whole survive the gain, loss or replacement of parts? Philosophers have been interested in such questions since Plato and the interest continues in contemporary metaphysics. In this chapter, I want to look at some of the ways in which philosophers have thought about parts and wholes. My aim is to see if any of the available part/whole distinctions can help us distinguish animals that are merely partially composed of human parts from animals that are part-human.

I begin with *mereology*, a metaphysical theory of the relations of parts to wholes. I then look at an applied form of mereology, *bio-ontology*, which is intended to capture the unique nature of parts and wholes in biology. In the next section, I consider an *intuition-based* approach to parts and wholes, which is an approach that has become the default strategy for delineating part-humans in bioethics. Finally, in the last two sections, I examine two

part/whole distinctions often used to help categorize biologically engineered animals. The first is a *quantitative* approach, by which the degree of humanness is calculated via the ratio of human to nonhuman parts. The second is the *germ-line/soma distinction*, an approach which emphasizes placement instead of number of human parts in the genetically engineered animal.

Mereology

Mereology is a metaphysical theory of the relations between parts and wholes. Although philosophers have been thinking about parts and wholes for a long time, the pure theory of part-whole relations was first formulated by Stanislaw Lesniewski in 1916. The theory did not become accessible to English speakers until the publication of Henry Leonard's and Nelson Goodman's *The Calculus of Individuals* in 1940. In what follows, I focus mostly on the contemporary formulations of mereology as they grew out of the Lesniewski, Leonard and Goodman tradition.

Mereology is structured in a way similar to logic: it is a theory based on axioms and derived theorems. For example, any mereological system requires at least one primitive binary relation. Most often this relation is Parthood where "x is a part of y" is written Pxy. Using the Parthood relation, one can establish some basic axioms. For instance, in standard mereology there is the axiom of Reflexivity:

Reflexivity (Pxx): Everything is a part of itself

And the axiom of Transitivity:

Transitivity ((Pxy & Pyz) → Pxz):

Any part of any part of a thing is itself part of that thing

Additional axioms and principles are then added by invoking the existence of certain mereological items given the already established existence of other items. For example, standard mereology includes the Unrestricted Composition Principle, which states that there is always a mereological sum of two or more parts:

Unrestricted Composition:

For all xs there is some y such that the xs compose y

In other words, for any number of objects there exists a mereological sum that consists of exactly those objects. For example, besides the 52 cards that make up a deck, there also exists something else that the cards compose, namely a deck.

Focusing on the Unrestricted Composition principle helps reveal the similarity between mereology and set theory. A set is determined precisely by

what is in it. The same is true of mereological sums. Thus, in set theory, playing cards can compose a set but so can my left shoulder, a bottle of water and an accordion. There need not be any common property that members of a set share in order to be part of one set. Similarly, as the Unrestricted Composition principle demonstrates, there need not be a common property that objects share in order to compose a mereological sum.

Rather than getting lost in the details of mereology and set theory, perhaps a more efficient way of assessing the applicability of mereology to part-humans is to think about the following question. Do we run into any problems if we conceive of organisms as sets composed of various members or, in mereological terms, as sums composed of various parts? The suggestion to conceive of organisms as sums might seem bizarre given Ghiselin's (1974) and Hull's (1978) influential thesis that organisms and species should be treated as individuals rather than classes. However, sets differ from classes in the following way: While a class is a collection of objects whose members *share a common property* the same requirement does not apply to sets. Consequently, although Ghiselin and Hull object to defining organisms in terms of shared cellular properties and to defining species in terms of shared intrinsic properties, that objection has no force when biological entities are considered sets. After all, sets are defined precisely by what is in them, which means that even if there is no intrinsic property that all the parts of an

organism share, the organism can still be considered a set—a set of whatever parts comprise that organism.

Hence, although conceiving of an organism as a sum of parts may not be very interesting or informative, doing so does not commit us to anything that is in tension with the biological nature of organisms. However, the noncommittal aspect of mereological sums no longer holds true when we consider another principle of mereology based on an analogous principle in set theory:

Extensionality: Sameness of parts is sufficient for identity

The mereological Extensionality principle says that an object is exhaustively defined by its constituent parts. In set theory, this principle states that a set is exhaustively defined by its constituent elements. What this means is that if one set has four telephones in it (and nothing else) and another set has four telephones in it (and nothing else) then they are the same set if they contain the same four telephones. Otherwise they are different sets.

If we apply the principle of Extensionality to organisms, two problems emerge. First, organisms with different parts at different times will not be the same organism. This results from the fact that, on the Extensionality principle, an object with different parts at different times cannot be identical with the sum of its parts at any other time (Simons, 1987). Let me explain

what I mean when I say that organisms have different parts at different times. At the beginning of the life cycle, an organism is composed of cells that contain structures that will also appear in the adult form of the organism, e.g., chromosomes, mitochondria, membranes, etc. Yet, as the organism grows it acquires new parts such as organs, bones, limbs—parts that were not present at the embryonic stage. For example, in our own species, females gain breasts after puberty and if they become pregnant, they will grow a fetus. On the other hand, both men and women lose parts, e.g., the tissue lining the intestines is exchanged every few days, and after puberty, women lose an egg every month they are not pregnant. Perhaps the most striking examples of an organism's capacity to lose and gain parts are organisms that go through dramatically different life stages. For example, the butterfly goes through the egg, larva, pupa, and the adult stage.

The point is that the process of gaining and losing parts is not something that is a rare exception for organisms. It is what organisms do! They grow, reproduce, age—the life cycle is about change, almost by definition. Hence, while it might make sense to identify a set with the sum of its members, given the static nature of sets, to apply the Extensionality principle to organisms is to violate the idea that organisms retain their identity through time. A criterion according to which sums composed of different parts are different is fundamentally incompatible with the workings of the biological world.

The second problem that organisms pose for the Extensionality principle is that an organism is fundamentally different from its disassembled parts—something that the Extensionality principle does not recognize (Koslicki, 2008). According to the Extensionality principle, if x and y have all their parts in common then x and y are identical. Hence, if I were to take my cat, cut her open, remove her liver and heart, and place the two organs along with the rest of her body in a large zip lock bag, the Extensionality principle would lead me to think that the contents of the bag are identical to my cat before the procedure. Similarly, if I were to chop up my next door neighbor at the joints and stack up all his body parts in the corner of the backyard, the heap of body parts would be identical to my neighbor given that all of his parts are contained in the heap. As strange as this principle may seem when we apply it to organisms, it makes perfectly good sense when we apply it to sets. Given that a set has no properties other than its members, a set is exhaustively defined by its constituents. The relationships that the members of a set bear to each other are irrelevant to the identity of the set.

It seems obvious, however, that the same does not hold true for organisms. To equate a heap of my neighbor's parts with my neighbor—prior to the massacre—seems very strange, precisely because the arrangement and the relationship between the parts of an organism do matter. Even when the organism is still alive, a change in the arrangement of the parts can have

dramatic effects on the organism as a whole. Imagine what the rearrangement of organs would do to an organism or what the rearrangement of nucleotides within the coding sequence of its DNA would do. If on the Extensionality principle, sameness of parts is sufficient for identity and the arrangements of parts is irrelevant, the principle is violated the moment we consider living entities.

To be fair, mereologists are concerned with relations among parts, but their concern is very different from the concern biologists share when they discuss the relationship between organisms and their parts. Talk of relations and integration among parts in standard mereology is motivated by the problem of *arbitrary sums*. The arbitrary sums problem arises as a consequence of accepting the Unrestricted Composition principle that, if you recall, states that for any number of objects there exists a sum that consists of exactly those objects. This principle generates the problem of the existence of certain gerrymandered, mereological sums for whose existence there is no evidence outside of the theory itself. Hence, the Mormon Temple and the Pope comprise a mereological sum and there exists a "trout-turkey" (David Lewis's example (Lewis, 1991, pp. 79-81)) whose parts are the still undetached upper half of a trout along with the still undetached lower half of a turkey. The problem of arbitrary sums cannot be easily fixed by adding a requirement of spatio-temporal proximity. Why? Because such an arbitrary requirement would not exclude pluralities of objects that are gerrymandered

but happen to be connected in space and time. Van Inwagen (1990) demonstrates this point with an example of a handshake. Based on the spatio-temporal proximity requirement, two people shaking hands would compose a further object for as long as they are engaged in the handshake simply because their hands are touching (Inwagen, 1990). Thus, when mereologists talk of relations and integration among parts they are doing so with the aim of solving problems of this kind. Biologists, on the other hand, care about the integration among parts because they are interested in explaining how the parts contribute to the functioning of the organism.

There was a time when an effort was made to make mereology more suitable for dealing with organic wholes. In the mid 1950s, Nicholas Rescher and Paul Oppenheim wrote a paper that was an attempt to tamper with the axioms of mereology in order to "accommodate a wide portion of the spectrum of scientifically interesting usages of 'is a part of'" (Rescher, 1955, p. 8). Rescher and Oppenheim put together a short list of requirements that a mereological sum should meet in order to count as an integrated whole (e.g., an organic whole):

i. The whole must possess some *attribute* in virtue of its status as a whole—some attribute peculiar to it, and characteristic of it as a whole.
ii. The parts of the whole must stand in some special and characteristic *relation* of dependence with one another; they must satisfy some special condition in virtue of their status as parts of a whole.
iii. The whole must possess some kind of *structure*, in virtue of which certain specifically structural characteristics pertain to it. (Rescher & Oppenheim, 1955, p. 334)

However, one could not easily transfer these requirements to mereological theory unless the concepts of *attribute, relation* and *structure* were defined formally. The formal aspect of mereology is considered a virtue of the theory because it means that mereology (like logic) is without content and can therefore be applied to anything. But when formal considerations are applied to the plethora of phenomena found in the world, we discover that the only way mereological axioms can capture the messiness of reality is by leaving all the mess out.

Consider the special sciences that concern themselves with particular (and messy) kinds of composition relevant to their respective domains. Biologists are interested in how cells compose multicellular organisms, chemists in how oxygen and hydrogen compose water, economists in how individual markets compose economies, etc. But mereologists are not interested in such details. After all, to include them would be to lose the formal aspect of their theory. Rather, they seek to understand something more fundamental: the general composition relation itself (Ladyman, Ross, Spurrett, & Collier, 2007). This is the relation that obtains between parts of any whole. Mereologists call it "fusion." The problem is that by making fusion *the* abstract composition relation, mereologists are ignoring actual complexity (of course, the more obvious problem is that we have no reason to believe that anything like fusion actually exists).

The difficulty of extending a formal theory like mereology to accommodate the messy nature of organisms is what ultimately led mereologists to give up on the Rescher and Oppenheim project. Simons summarizes this historical attempt with little hope for the future,

> The lesson of history seems to be that philosophers who have talked about integral or organic wholes…have never managed, even where they tried, to get very clear about what such a whole was, which may suggest that the whole area is better left alone. (Simons, 1987, p. 290)

Despite Simons's suggestion—to leave organic wholes out of mereology—a new subfield of mereology, known as bio-ontology, has recently emerged. Customized to the world of biology, bio-ontology is designed to capture the variable and complex nature of organisms. In the next section, I provide an overview of bio-ontology and assess its viability as a strategy for investigating the nature of part-humans.

Bio-ontology

Similar to standard mereology, bio-ontology (sometimes referred to as "applied mereology") is a metaphysical theory concerned with the relations between parts and wholes as well as the relations between parts within a whole. What is different about bio-ontology, however, is that its primitive relations are applicable to the world of biology. Unlike the primitive relations in standard mereology—that are based on logical relations—the primitive relations in bio-ontology are "law-like relations between universals of the sort

that are discovered through scientific research" (Smith, 2004, p. 324). Consequently, the relations used in bio-ontology hold between classes, not sets. Nonetheless, bio-ontology is similar to mereology in that it is a formal theory; its entities are represented by logical statements that describe what the terms are, how they are related to one another, and how they can or cannot be related to one another.

The two primitive relations in bio-ontology are 1) "is_A," the relation of identity and 2) "part_of," the relation of parthood. Since any relation in bio-ontology is a law-like relation between universals, the relations hold between classes. Thus, A is_a B is read "the class A belongs as a subclass to the class B" or "the class B subsumes class A." What the A is_a B relation implies is that if (i) class A belongs to class B and (ii) a certain particular is classified as being an A then (iii) it has to be classified as being a B, too (Johansson & Lynöe, 2008). If we substitute 'cat' for A and 'mammal' for B we get the following example: if (i) cats are mammals and (ii) Felix is a cat then (iii) Felix is a mammal. This is what the bio-ontological claim "cat is_a mammal" implies.

The part_of relation used in bio-ontology is also a relation between classes. What the claim A part_of B implies is that each member of class A is part of a member of class B, but not all members of B have a member of A as a part. For example, the bio-ontological claim "nuclei part_of cells" is true

because all nuclei (A) are parts of cells (B) but there are cells that do not have nuclei, such as prokaryotic cells.

Since the relations used to describe biological entities in bio-ontology are relations between classes it will be helpful to once again review the difference between classes and sets. Recall from the last section that a set (used in standard mereology) is defined precisely by what is in it while a class (used in bio-ontology) is a collection of objects that share a common property. Accordingly, there can only be one empty set, i.e., a set without a member, while there are many empty classes, e.g., the class of mermaids and the class of offspring of two mules. The two are different empty classes but they count as one and the same empty set (Johansson & Lynöe, 2008). Moreover, classes in bio-ontology have no predetermined limits in space and/or time. For example, the class of cats is "open" in a sense that if a new cat is born it automatically becomes a member of its corresponding class. Finally, entities referred to in bio-ontological claims are "prototypes," i.e., they are more or less similar to each member of the class they represent (Johansson & Lynöe, 2008, p. 431). Hence the claim "fingers part_of hand" refers to the prototypical five-fingered human, although nonprototypical hands also exist and may have more or less than five fingers.

When I first compared the concept of a set to that of a class, in the last section, I brought up Ghiselin's and Hull's influential thesis: that organisms and species are individuals rather than classes. Although the "individuality

thesis" did not pose a problem for mereology, because relations in mereology hold between sets, it poses a problem for bio-ontology, because relations in bio-ontology hold between classes. I will now reconstruct Ghiselin's and Hull's argument in order to show why a bio-ontological account of a "cat"—where to be a cat is to be a member of a certain class—is incompatible with Ghiselin's and Hull's account of what it means to be a cat.

Ghiselin (1974) and Hull (1978) claim that species are individuals rather than classes by arguing that species are entities capable of evolving by selection. The implication is that such evolution requires organisms of a species to be connected by parent-offspring relations and these relations, in turn, require that the organisms of a species be spatiotemporally connected. As a result, members of a species must be generationally continuous if there is to be evolution by natural selection operating across generations—they must be part of a single evolving lineage (Ereshefsky, 1991; 2008). Now, since individuals consist of parts that are spatiotemporally restricted and because classes, on the other hand, consist of members that are spatiotemporally unrestricted (Instances of gold, for example, can occur anywhere and still belong to the class "gold."), species are more likely to be individuals than classes.

This is especially true in bio-ontology. Classes are groups of entities that function according to scientific laws. These laws have no limits in space and/or time, which means that if "all cats are mammals" is a law, then that is

true of any cat that is born anywhere at any time. But if species are individuals, they do not function according to scientific laws. In fact, a shared similarity among organisms belonging to a particular species can be misleading. Two organisms may be very similar but unless they belong to the same spatiotemporally continuous lineage they are not part of the same species. As Hull (1986) argued, from an evolutionary perspective there is no nonhistorical similarity, governed by a scientific law, that all and only humans must share to be part of the species *Homo sapiens*. Being a part of the lineage *Homo sapiens* is both necessary and sufficient for being a human. Thus, the following statement in bio-ontology, "all humans are x" where x is a similarity that has the properties of a scientific law, is simply not a true statement about our own species.

The use of a prototype in bio-ontology further exemplifies the incompatibility between the theoretical commitments of bio-ontology and the "species are individuals" thesis. If you recall, the idea behind prototypes is that they are able to represent a class insofar as they are more or less similar to each member of that class. But if species are individuals then an organism belongs to a species because it is part of a lineage not because it resembles other members of that species. This is why species are not represented by prototypes but by "type specimen." The type specimen serves as an ostensive definition of a species: a definition that conveys the meaning of a term by pointing to an example. The type specimen for the species *Homo*

neanderthalensis, for instance, was the specimen "Neanderthal-1" discovered by Johann Karl Fuhlrott in 1856, consisting of a skullcap, thigh bones, part of a pelvis, some ribs, and some arm and shoulder bones (Richards & Schmitz 2008). Neanderthal-1 "defined" the species *Homo neanderthalensis* insofar as it pointed to the species of which it was a member. Unlike a prototype, the type specimen need not be similar to other members of its species. It can be aberrant, deformed or have color variations because there is no requirement for it to be "typical" of the species. It needs only to be appropriately causally connected.

The fact that relations in bio-ontology are between classes rather than individuals is reason enough to worry about the applicability of bio-ontology to the biological domain. However, there are other aspects of bio-ontology that appear to be especially fitting for analyzing the nature of part-humans and, consequently seem worthy of a closer look.

For example, one promising aspect of bio-ontology is that it provides guidelines for deciding when something is a genuine *part of* an organism rather than something that is merely *located in* it. Consider the act of eating a banana as a useful demonstration of the transition from location to parthood. When I bite into a banana, a piece of it is no longer a part of the fruit but is now located in my oral cavity. It then degrades into sugars, amino acids and fatty acids. The portions that traverse the epithelium become parts of epithelial cells and then parts of the blood and lymph nodes. Others might

not acquire the status of parthood but will remain merely located in the stomach cavity (Smith, Majino, Schulz, Kumar, & Rosse, 2005). Bio-ontologists employ various criteria for establishing whether something is a genuine part of an organism or something that is merely located in it. Such criteria may be useful for judging whether an animal is merely partially composed of human parts or part-human, which is why I now turn to the two most widely used parthood criteria in bio-ontology—the *genetics* and the *function* criteria.

According to the genetics criterion, any biological object A is merely located in B (i.e., not part of) if genetic origins of A and B are different (Schulz, Kumar, & Bittner, 2006; see also Smith et al., 2005). In other words, if something is to count as part of the body it must be of the same genetic origin as the body itself. This means that an embryo is not part of the mother, and a bacterium is not part of a tissue. The two are merely located in the body given that their genetic origins are different than the body itself. In addition, artifacts such as a heart pacemaker, bullet and dental filling are also not part of the body since they have no genetic origin.

The second widely used parthood criterion is that of function. According to the function criterion, A is part of B if A has a function essential to B's survival or the maintenance of B's proper functioning (Schulz et al., 2006; see also Smith et al., 2005). According to the function criterion, the brain and the heart are part of an organism because they both perform functions essential for the survival of the organism. Conversely, urine is not

essential to the survival of the bladder, which means that urine is not part of the bladder but is merely located in it (Smith et al., 2005).

While the genetic and function criteria have potential to be legitimate ways of establishing genuine parthood, their potential remains unrealized because they are simply asserted, rather than argued for, in the bio-ontology literature. What is more frustrating, however, is that the authors allow for exceptions to the criteria if the entity being considered seems *intuitively* to be part of the organism. For example, sugars, lipids, amino acids, oxygen and nitrogen molecules do not have a genetic origin, which means that they ought to be merely located in an organism on the genetics criterion for parthood. But when we think of a banana being broken down into amino acids, the portion of which traverse the epithelium and ultimately enter the blood stream, intuitively it seems that the amino acids *do* become part of the organism. Consequently, the genetics criterion for parthood is overruled by an appeal to intuitions (Schulz et al., 2006). The same exception applies to cell organelles such as chloroplasts or mitochondria (i.e., endosymbionts) that have their own DNA, and thus a different genetic origin than the host cells, yet are considered parts of cells by some bio-ontologists (Schulz et al., 2006; see also Smith et al., 2005).

Exceptions to the function criterion also apply. They include kidneys or other organs that come in pairs, the appendix whose functional relevance has disappeared during evolution and hair, which seems inessential to the proper

functioning of the body. None of these entities would count as parts of the body on the function criterion since, by themselves, they are not essential to its proper functioning. But, here again the intuitions of bio-ontologists overrule the parthood criterion because treating these entities as merely located in the body seems counter intuitive (Schulz et al., 2006; see also Smith et al., 2005).

Additional problems arise when an entity is considered merely located in the body on one criterion but a part of the body on the other. A transplanted heart valve or kidney, for instance, is merely located in the body on the genetic criterion since its genetic origins are different than that of the recipient. Yet transplants and implants often fulfill the same essential biological function as genetically identical structures. Thus, on the function criterion, they would count as part of the body (Schulz et al., 2006). Even if bio-ontologists were not committed to using both criteria at all times, they still fail to provide overriding reasons to help resolve conflicts of this kind. In other words, they fail to provide reasons for why sometimes the genetic criterion should overrule the function criterion and vice versa

The fact that the genetic and the function criteria allow for exceptions based on intuitions and that no overriding reasons are provided when the two are in conflict is certainly troubling. But further problems arise when we take a closer look at the function criterion. Recall that the function criterion for genuine parthood states that A is part of B if A has a function essential to B's

survival or to the maintenance of B's proper functioning. A virus, for example, may take on a functional role in a body, directing the cell to construct certain proteins that the virus needs for reproduction, but it is not part of the body on the function criterion because the directions given by the virus interfere with the body's proper function (Donnelly, 2004). But what exactly is the body's proper function? The function debate in philosophy of biology is the place to look for answers.

Although in the bio-ontology literature the word 'function' is often preceded by the word 'proper,' bio-ontologists explicitly state that their account of function is descriptive rather than normative: "In conformity with the views of Cummins…we insist that much function talk is either purely descriptive or explains how something works when it exists" (Johansson et al., 2005, p. 163). Since the notion of function endorsed by bio-ontologists "conforms" to the views of Cummins, let us start there. According to Robert Cummins (1975), function statements explain the contribution of an item to the capacity or activity of the system that contains the item. Hence, on Cummins's view, the function of an item does not explain the existence of the item; rather, the function of an item is merely its causal contribution to the system.

Cummins's notion of function seems right insofar as it accurately describes the way in which biologists provide a functional analysis of an organism—they conceptually decompose the organism into simpler parts and

describe what each part contributes to the overall capacities or activities of the organism (Neander, 1999). In physiology, for example, the human organism is decomposed into systems (e.g., digestive, circulatory, respiratory, reproductive, immune, etc.), these systems are then decomposed into their parts (e.g., the digestive system into the mouth, esophagus, stomach, pancreas, etc.), these parts then further decomposed into their parts (e.g., the mouth into the tongue, saliva glands, teeth, etc.) and these into theirs (e.g., the tongue into muscles, sensory receptors, etc.) down to the level of individual cells and their subcellular components (Neander, 1999). As the organism is conceptually decomposed, the causal contribution of each part is described along the way.

But some have questioned whether identifying causal contributions in biology can be nonteleological in the way Cummins describes. For example, David Hull (1974) demonstrates how the concept of function in biology is inevitably teleological by contrasting a physicist's explanation of the expansion of gas with a biologist's explanation of sweating in mammals

> Just as a physicist might say that heating a gas causes it to expand, a biologist might say that heating a mammal causes it to sweat. But a biologist might also say that a mammal sweats when heated in order to keep its temperature constant, while no physicist would say that a gas expands when heated in order to keep its temperature constant—even though that is exactly what happens. (Hull, 1974, p. 102)

Hull's point is that keeping the temperature constant is *not* the function of gas expansion but simply its effect, while keeping the temperature constant

is the function of sweating in mammals. Why do we attribute a function to the sweat of a mammal and not to the expansion of gas? According to David Buller (1999), the difference lies in the theoretical commitments implicit in the biological concept of function. What accounts for the difference is that sweating, like all biological functions, is a goal-directed process. Sweat seems to occur *in order to bring about* the cooling of the body while the expansion of gas does not seem directed toward the goal of maintaining temperature (Buller, 1999).

Cummins's notion of function—as mere causal contribution—does not capture this teleological component unique to biological function. It also does not provide any means of discriminating between functions and mere effects. On Cummins's account, pumping blood need not be the heart's function. It could also be making noise (something a heart does). Hence, we could say that the mammalian circulatory system has the capacity to make noise, and on Cummins's functional analysis, it would follow that the heart contributes to the mammalian circulatory system by making noise (Buller, 1999). But no biologist would claim that making noise is the function of the heart. Hence, if on Cummins's view, to say "the function of X is Y" is to mean "X produces the effect Y" then his account of function fails to distinguish between the effects of an organ, such as making noise, and the organ's function, such as pumping blood (Buller, 1999). Lastly, if functions are capacities, as they are on Cummins's view, then the human body's capacity to die of various diseases

would count as a function in the same way that a body's capacity to survive would count as a function (Griffiths, 1999).

In addition to these problems, the notion of function that bio-ontologists endorse is also allegedly a "purely descriptive" notion. But if bio-ontologists were right, that function is purely descriptive, then a heart that does not pump blood would not have that function. But notice that we assign the function of pumping blood to a heart even if it fails to do so. We call such hearts diseased, malformed, injured, broken, etc. because they are unable to perform the function that they are *supposed to* perform (Millikan, 1989). As Karen Neander points out, the same applies to artifacts, "a brake is a brake in virtue of what it is supposed to do—was intended or designed to do—not in virtue of having some specific structure or disposition" (Neander, 1999, p. 226). Furthermore, the function of an organ sets the norm for what it is to function adequately. A heart does not perform its function well if it pumps blood around in a manner that is too slow to deliver enough oxygen to the inner organs of an organism (Wouters, 2005). In short, what makes it legitimate for us to expect from any heart that it pumps blood in a certain way is the fact that functions are *normative*, not descriptive.

If biological function is something that is *supposed to* happen *in order to bring about* some result then a theory of function needs to explain how normativity and teleology are possible in nature (Buller, 1999). To date, Ruth Millikan's (1984) etiological account is considered to be one of the best

attempts at demystifying these peculiar features of biological function. Millikan defines the function of an item in terms of its evolutionary history. On her etiological account, to ascribe a function to an item is to claim that earlier items of the same type had this effect and that their having this effect explains the presence of later items of the same type (Griffiths, 1999). Hence, the function of the heart is to pump blood because pumping blood is what our ancestors' hearts did, and it is what caused these ancestors to be selected over competitors that lacked hearts or in which the heart had a different form (Wouters, 2005). Hence, if we say that the function of a cat's sharp curved claws is to catch mice it need not be the case that the cat's claws were *designed* in this way *for a purpose*. Instead, we can assume the etiological account of function and say that catching mice is the function whose survival value has bred cats with this particular form of claw (Lorenz, 1963, p. 9). After all, on Millikan's account, a trait or organ has a function in virtue of its role in the process of natural selection—to say that the function of X is to do Y implies that X is there because *its ancestors* did Y (Griffiths, 1999; see also Millikan, 1984; Neander, 1983; Wimsatt, 1972; Wright, 1973, 1976).

There is some consensus among philosophers of biology that the theory of evolution by natural selection can demystify the normative and teleological features of biological function (although, as is always the case in philosophy, some would disagree (cf. Cummins, 1975; Davies, 2001; Hardcastle, 1999)). Moreover, unlike Cummins's theory, Millikan's theory can distinguish

functional effects from accidental ones. On the etiological account, the reason that it is the function of my heart to pump blood rather than to make noise is because the hearts of my ancestors contributed to their reproductive success, and thereby to the reproduction of hearts, by pumping blood, not by making noise (Buller, 1999). But bio-ontologists also reject the etiological account of biological functions, "Etiological approaches presuppose that all functional talk is explanatory talk; so that the function of A is referred to only in order to explain *why A exists*. Our attempt to defend a natural-scientific concept of function…rejects this presupposition" (Johansson et al., 2005, p. 163). It seems, then, that the bio-ontological account of function amounts to the following view. According to the function criterion, A is part of B if A has a function essential to B's survival or the maintenance of B's proper functioning. Hence, although a virus may take on a functional role in the body, directing the cell to construct certain proteins that the virus needs for reproduction, it is not part of the body on the function criterion because the direction given by the virus interferes with the body's proper function. What do bio-ontologists take "functions" to be? They insist that, in conformity with Cummins's view, functions can be purely descriptive. According to Cummins, the function of an item is merely its causal contribution to a complex system. The problem with Cummins's notion, however, is that it does not capture the teleological component of biological function, it fails to provide a means of discriminating between functions and mere effects, and it falsely

characterizes biological functions as something descriptive rather than normative. Millikan's etiological account, on the other hand, avoids these shortcomings and is considered to be the best attempt at demystifying these peculiar features of biological function. However, bio-ontologists reject the etiological account leaving them with a notion of function that is hard to defend.

Intuitions

Although the axioms of mereology and bio-ontology are based on the rules that govern sets and classes, it is with the help of *intuitions* that the metaphysicians working in these areas decide which theories to accept and which to reject. By "intuitions" I mean judgments that are not made on the basis of an explicit reasoning process that a person can consciously observe (Gopnik & Schwitzgebel, 1998). In metaphysics, it is considered a cost to a theory, rather than a benefit, if one is forced to abandon some intuition in order to accept the theory. The metaphysics literature is full of arguments against theories that lead to unintuitive consequence and of arguments that compare theories on the basis of the quantity and quality of the intuitions with which they conflict (Ladyman et al., 2007). For example, consider the following passage from L.A. Paul (2004) on the role of our intuitions in establishing the essential properties of objects:

> This is a serious problem for the essentialist if she thinks that an object's nature is not adequately captured by the few essential properties we have reasonably clear intuitions about. As such an essentialist, I take the variability of our intuitions about which properties of objects are essential to constitute the most serious threat to essentialism. After all, essentialism has a solid intuitive grounding as part of a philosophical (and perhaps even somewhat pretheoretical) understanding of the world, and the success of quantified modal logic has provided a rigorous formal framework that can undergird the view. But if, on gentle investigation, the intuitive grounding turns out to be confused or even absent, then the robust ontological picture of the *de re* natures of objects that essentialism entails may be more costly than it is worth. (Paul, 2004, p. 178)

As Paul points out, the fact that our intuitions about what properties of an object are essential to it may vary is a serious problem for "essentialist" metaphysicians. After all, metaphysicians believe that our intuitions ground our philosophical understanding of the world. Given the prominent role of intuitions in metaphysics, it makes sense for those working in mereology and bio-ontology to formulate the kinds of theories that reassure them of what they already believed to be true.

Of course, contemporary metaphysicians are not the only ones who appeal to intuitions in constructing and arguing for their theories—philosophers have been doing it since Plato. Recent philosophical literature driven in large part by appeals to intuitions includes: analyses of knowledge, the nature of meaning and reference, the human mind, and the moral right and wrong. What ought to be the proper role of intuitions (if any) in the validation of philosophical theories is a highly contentious topic (see, for

example, DePaul & Ramsey, 1998). I do not wish to fully engage in this debate. Instead, I want to offer a couple of reasons against the sole reliance on intuitions. My critique has two targets. The first one, as I already mentioned, is standard and applied mereology. The second one is bioethics, where intuitions have become the default strategy for assessing the humanness of biologically engineered animals.

As I explained in the last two chapters, successfully transplanting human parts into different species is a relatively recent phenomenon. The infancy of the research program might explain (although not justify) why for some bioethicists, intuitions have become the default method for assessing the relative humanness of genetically engineered animals. Consider, for example, an article by Josephine Johnston and Christopher Eliot in which the authors claim that "a human being with functional eagle wings" would likely count as human (Johnston & Eliot, 2003). The authors provide no justification for this claim. They assume that readers will find it *intuitively* true. Or, again, consider a report about the ethics of transplanting human neurons into a mouse (see Chapter 6). At Stanford University, an ethics committee wrote:

> We can note that, as far as we can see, the concern must be about specific kinds of human characteristics. A mouse with the human brain's sense of vision does not seem particularly troubling. Even a mouse with a memory of human quality might not be a concern. But a mouse with human language capabilities

> or that seemed to have a human level of self-consciousness would be, at the least, troubling. (Greely, Cho, Hogle, & Satz, 2007, p. 38)

The claim that some mice with human characteristics might be more human than others—and thereby more troubling—is, again, justified only by an appeal to intuitions. In fact, the committee recommends using thought experiments about mice with various human characteristics as a "useful way to explore these problems" (Greely et al., 2007, p. 18).

Although there is nothing *prima facie* wrong with using intuitions in the course of investigation, I want to offer a couple of reasons against the sole use of intuitions in the context of part-humans and, more broadly, in the context of metaphysics. First, evidence from psychology (Nash, 1974) suggests that when it comes to judging the humanness and the "animality" of part-human, part-animal mythological hybrid figures our intuitions run contrary to our reasoning. A random sample of college students asked to judge a figure's humanness or animality claimed that they were especially influenced by the humanness or animality of the head or face. However, when the same subjects were asked to judge 29 portraits of mythological hybrids along a human-animal continuum they consistently judged the animal-headed figures having a human torso and limbs as clearly more human than human headed figures having an animal torso and limbs (Nash, 1970). What this study suggests is that the subjects' *intuitive* designation of mythological hybrids along a human-animal continuum was contrary to their *reasoned*

view of what body parts should have the most influence on their decisions. The apparent inconsistency between intuition and reason is likely to recur in judgments of the humanness of biologically engineered animals, since both mythological hybrid figures and part-human candidates are comprised of human and nonhuman parts.

The second problem with relying on intuitions when delineating part-humans is that human intuitions about a wide range of empirical facts have frequently turned out to be wrong. History has shown that intuitions about the nature of the solar system or the shape of the earth have been mistaken. In fact, intuitions about empirical facts continue to mislead us even today. Recall the 1997 photograph of a hairless mouse with what appeared to be a human ear growing on its back (see, for example, Renneberg & Demain, 2007). The photograph prompted protests around the world against genetic engineering because the people protesting had falsely assumed that the mouse was genetically engineered to grow a human ear on its back. In reality, however, no genetic engineering was involved in creating the mouse and the "ear" had no human cells in it (Choi & Vascanti, 1997). What appeared to be a human ear was only ear-shaped scaffolding made out of the same sterile, biodegradable material used in dissolving surgical stitches (Renneberg & Demain, 2007). Cartilage cells from the knee of a cow were then implanted into the scaffold, and the cartilaginous ear was implanted under the skin layer of the mouse. The mouse was immunodeficient, i.e., it

carried a random mutation that prevented its immune system from rejecting the cow graft (see Chapter 3). Eventually, the mouse grew extra blood vessels that infiltrated the biodegradable scaffolding and nourished the cow cells. Once the scaffolding had dissolved, the cartilage had enough structural integrity to support itself. The aim of the experiment was to grow a human body part that could be used in human reconstructive surgery, although this particular ear was never transplanted into a human since it was made out of cow rather than human cells.

One could argue that the above example is not a demonstration of the faults of our intuitions but rather a demonstration of how the media misleads us into believing something that is false. However, the point here is a broader one. Namely, that extrapolating our intuitions across unfamiliar territory (whether it is due to the media's influence or something else) can mislead us profoundly. Modern science has consistently confirmed this for scales, magnitudes, and spatial and temporal distances (Ladyman et al., 2007). For example, we are astounded to hear that there are more molecules in a glass of water than there are glasses of water in the ocean, or more cells in one human finger than there are people in the world. And no one's intuitions, in advance of the scientific findings, told them that combustion primarily involves something being taken up rather than given off, that white light would turn out to have compound structure, that birds are the only living descendants of dinosaurs, that the earth is round and moves around the sun,

or that Australia is presently on its way to a collision with Alaska (Wolpert, 1992; Ladyman et al., 2007). The point is that scientific findings often run counter to human intuitions.

To summarize, in this section I have presented two reasons against the sole use of intuitions as an investigative strategy. First, evidence from psychology suggests that when it comes to judging the relative humanness of part-human hybrids, our intuitions run contrary to our reasoning. Second, human intuitions often mislead us when we rely on them to make judgments about empirical facts. I aimed my critique at mereology and bio-ontology, two areas where theories are accepted based on how well they align with our intuitions, and bioethics, where intuitions have become the default method for assessing the relative humanness of genetically engineered animals.

Quantitative

In the next two sections I turn to a couple of different approaches to thinking about parts and wholes that on their face seem more appropriate to delineating part-humans than the previous approaches I looked at (that were simply made available by philosophical theory). The quantitative approach, unlike the intuition-based approach, involves explicit reasoning about transferred human parts. Here, the degree of humanness found in an organism is calculated via the ratio of human to nonhuman parts. Sina Muscati characterizes this approach in the following way:

> A quantitative model would focus on the proportion of human genetic material in the transgenics. This approach would involve setting an arbitrary threshold of prohibited "humanness"—at transgenics having 50% or more human genes, for example, or perhaps 25%. (Muscati, 2004, p. 216)

According to Muscati, the quantitative model involves measuring the number of human cells or genes transferred and then calculating the final proportion of human to nonhuman cells or genes in the recipient. It also requires setting a threshold to determine which organisms are part-human and which ones are merely partially composed of human parts. If the threshold is set to 50%, an organism with less than 50% human genes or cells is merely an organism partially composed of human parts. More than 50%, the organism is part-human.

The quantitative method is straightforward but it has several obvious drawbacks. First, if proportion of human to nonhuman cells is the primary concern, then a typical healthy adult would be more nonhuman than human. This follows from the fact that the body of a healthy human adult has an estimated 10 times the number of microbial cells as human cells—the small size of the microbial cells, compared to human cells, accommodates their large number (Singer, 2007; Dupré, 2010). Consider, for example, that the aim of the Human Microbial Project (HMP), an extension of the Human Genome Project (HGP), is to count and characterize all the microbes living in the human body, paying special attention to the microorganisms living in the nasal passages, oral cavities, skin, gastrointestinal tract and urogenital tract

(Turnbaugh et al., 2007). Since the percentage of microbial cells will definitely be higher than the percentage of human cells in a typical human being, establishing the humanness of a chimera by counting how many of its cells are human will not be very informative. On the other hand, when it comes to counting human genes instead of cells, the problem seems to go in the opposite direction. In light of evolutionary conservation, most human genes are shared with a variety of organisms, which means that on the quantitative model, many of these organisms would count as part-human long before they were ever tampered with in the laboratory.

An additional problem facing the quantitative model is that differences counted at the molecular level do not add up to differences at the level of the phenotype. The part-whole relationship of organic wholes is far more complicated. Consider that at the beginning of the life cycle—the embryonic stage, which, if you recall, is also the stage at which most biological engineering is conducted—an organism is composed of cells that contain structures that will appear in the adult form of the organism, e.g., chromosomes, mitochondria, membranes, etc. (Godfrey-Smith, 2001) Yet as the organism grows it acquires new parts such as organs, bones, limbs—parts that were not present at the embryonic stage. Naturally, the parts that *were* present at the embryonic stage had much to do with the parts acquired later in life but just how much is not known. What is known is that the relationship between the early parts and the later parts is not one-to-one:

one gene can contribute to multiple phenotypes and many genes can collectively contribute to one phenotype. To complicate matters further, the developmental response of genes to a changing environment is nonlinear and does not allow for the simple ordering of genes along a one-dimensional scale phenotype (Lewontin, 2002). Thus, adding up the number of human genes or cells in an organism is not going to reflect the amount of human traits found in the organism as a whole.

Given the ratio of human to nonhuman cells in the human body, the high number of conserved genes among various organisms, and the complicated relation between organic wholes and their parts, the quantitative model is unlikely to be a good measure of the level of humanness found in any given organism. But perhaps the most troubling aspect of this approach is the fact that setting a percentage threshold at the outset presupposes what is at issue, namely, what it means to be part-human.

Germ-line/Soma

Another approach to parts and wholes, often used to categorize biologically engineered animals is the germ-line vs. soma genetic modification distinction. The idea behind this approach is to pay attention to the location in the body where the human parts are being transferred, rather than simply counting how many are transferred. The germ-line vs. soma genetic modification distinction became popular in the 1970s, after the development

of recombinant DNA technology—the process used to transfer DNA from one organism into the DNA of another (see Chapter 3). Soon after, scientists became interested in using recombinant DNA technology to introduce non-mutated versions of disease-causing genes to achieve a therapeutic goal—known as "gene therapy" (Rasko, O'Sullivan, & Ankeny, 2006). Gene transfer procedures could result in either somatic modifications or germ-line modifications.

Somatic cells are all the cells in the body other than egg or sperm cells. (The term "somatic" comes from the Greek word *soma* for "body"). Hence, somatic genetic modification typically involves adding genes to the cells affected by a disease, e.g., liver cells affected by liver disease, with the hope of alleviating the disease. The new genes are not passed on to future generations. Unlike somatic cells, the germ-line "constitutes the reproductive cells of an organism (i.e., the germ cells, including their products, and gametes) that transmit genetic information from one generation to the next" (Rasko et al., 2006, p. 6). Hence, germ-line genetic modification typically involves adding genes to the egg, sperm or very early embryos, with the hope of curing a disease. As a result, the modified genes would likely appear in all the cells of the offspring and in all subsequent generations of that offspring.

Experimental somatic modification has been performed on humans, although it has not proven very successful in clinical trials. In 1999, somatic modification suffered a major setback with the death of 18-year-old Jesse

Gelsinger (Rasko et al., 2006). Jesse suffered from a rare enzyme disorder that affected his liver. As in all cases of somatic gene therapy, a virus was used as a vector to deliver the therapeutic gene to the affected cells. However, Jesse died from multiple organ failures soon after starting the treatment and it is believed that his death was triggered by an immune response to the virus carrying the therapeutic gene. However, in spite of this setback, research in human somatic gene therapy continues and is considered less controversial than germ-line gene therapy.

Germ-line gene therapy has the benefit of eliminating the disease before birth, but there are a number of reasons why it has not been performed on humans. First, there are safety reasons—germ-line genetic modification can introduce unwarranted mutations into the genome of the recipient. Second, there is a worry that "fixing" a genetic mutation before an individual is born will put pressure on parents to have "perfect" children, making germ-line genetic modification a form of enhancement rather than therapy. Finally, there is a concern that since germ-line modifications are inherited they could change the human gene pool and ultimately the whole human species. If we want to preserve the human gene pool, than we should outlaw human germ-line genetic modification, or so the argument goes. Whether this worry has any force is controversial. For example, Eric T. Juengst points out that "the human gene pool, unlike the sea, has no top, bottom, or shores; it cannot be 'preserved'" (Juengst, 2008, p. 156).

Putting gene therapy worries aside, the question of interest is the following: Can the germ-line/soma distinction help distinguish which genetically engineered animals are part-human and which ones are merely partially composed of human parts? At first, the distinction seems promising: if human genes are added to the germ-line of a nonhuman animal, or if human cells comprise the germ-line, then the animal might be considered part-human. Conversely, if human genes are merely added to a targeted area of cells, e.g., kidney cells, or if human cells only comprise the kidney, then the animal might be merely partially composed of human parts. But upon closer examination, it becomes apparent that the germ-line/soma distinction tells us very little about the humanness of the modified animal—if it tells us anything at all, it tells us something about the humanness of the future offspring of that animal. The reason why the germ-line/soma distinction is not helpful for delineating the humanness of genetically engineered animals is that scientists can control for tissue specific expression (Rasko et al., 2006). For example, they can control an experiment so that the germ-line modification is only expressed in the germ-line cells of the recipient and not any other cells. In this scenario, the only thing that would change would be the sperm or egg cells of the animal that have very little affect, if any, on the animal as a whole. Conversely, one can control the experiment so that somatic modification would be expressed in all of the cells of the recipient except its sperm or egg cells. Here, again, the germ-line/soma distinction

seems to fail: Why would we categorize an animal that is almost entirely composed of human cells—minus its sperm or egg cells—as merely partially composed of human parts? While the germ-line/soma distinction may be better-suited for examining the humanness of the offspring of modified animals—if the animals reproduce at all—it is not well-suited for examining the humanness of modified animals themselves.

Summary

In this chapter, I looked at some of the ways in which philosophers and scientists have thought about parts and wholes to see if any of the available part/whole distinctions would be helpful for distinguishing animals that are merely partially composed of human parts and animals that are part-human. I started with mereology—a metaphysical theory of the relations of part to whole and the relations of part to part within a whole. I argued that mereology is not equipped to capture the variable and complex nature of organisms because of its ties to set theory. Similar to set theory, mereology has an Extensionality principle, which states that an object is exhaustively defined by its constituent parts. However, contrary to this principle, an animal is identical with itself, even though it gains and loses parts in the course of its life and an animal is not identical to its disassembled parts, because the arrangement of parts is relevant to identity.

Next, I looked at bio-ontology, an applied form of standard mereology, especially designed to capture the variable and complex nature of biological entities. However, I was disappointed to discover that 1) bio-ontologists treat species as classes that have law-like relations, 2) their criteria of parthood are undeveloped, and 3) their account of function is questionable. In the next section, I considered an intuition-based approach to parts and wholes, an approach used not only in mereology/bio-ontology but also in bioethics. I found two problems with the intuition-based approach. First, evidence from psychology suggests that when it comes to judging the relative humanness of part-human hybrids, our intuitions run contrary to our reasoning; and second, human intuitions often mislead us when we rely on them to make judgments about empirical facts.

Finally, in the last two sections, I examined two part/whole distinctions often used to help categorize biologically engineered animals. The first was the quantitative approach, by which the degree of humanness is calculated via the ratio of human to nonhuman parts. I concluded that this approach is unlikely to be a good measure of the level of humanness found in any animal because of the surprising ratio of human to nonhuman cells in a typical human body, the high number of conserved genes among animals, and the complicated relation between organic wholes and their parts. The second was the germ-line/soma distinction, an approach that emphasizes placement instead of number of human parts in the genetically engineered animal. The

problem with this approach, however, is that while the germ-line/soma distinction may be well-suited for examining the humanness of the offspring of modified animals—if the animals reproduce at all—it is not well-suited for examining the humanness of modified animals themselves. In the next chapter, I propose my own approach to delineating part-humans, that avoids the problems of the approaches considered in this chapter.

CHAPTER 5

PART-HUMAN OR MERELY PARTIALLY COMPOSED OF HUMAN PARTS? MINIMUM REQUIREMENTS FOR MAKING THE DISTINCTION

Establishing what it means to be human, or part-human, in the age of advancing biotechnology is a difficult task. In the last chapter, I criticized a number of approaches that I thought were ill suited for the task of establishing the relative humanness of biologically engineered animals. In this chapter, I take on the less intimidating task of establishing *the minimum* that is required for an animal to count as part-human. I focus on "humanized mice," that carry a "partial or complete human physiological system" (Macchiarini, Manz, Palucka, & Shultz, 2005, p. 1307). As part-human candidates, humanized mice are supposed to make extrapolation[1] from mice to humans more reliable by simulating a variety of human diseases, e.g., diabetes (Leroith & Gavrilova, 2006), osteoporosis (Klein, 2008), Alzheimer's (Gotz, Schonrock, Vissel, & Ittner, 2009), etc. The purpose of the simulation is

[1] For more on the problem of extrapolation in biology see Ankeny, 2001; Bolker, 1995; Burian, 1993; Cartwright, 1989; LaFollette & Shanks, 1996; Love, 2009; Mitchell, 2000; Schaffner, 1986; Steel, 2008; Weber, 2005; Wimsatt, 1998.

to mimic human disease in the mouse in order to develop treatments for humans (cf. Chaible, Corat, Abdelhay, & Dagli, 2010; Rosenthal & Brown 2007; Shultz, Ishikawa, & Greiner, 2007).

As simulators of human disease, humanized mice need not exactly mimic the target human phenotype—only its relevant features. The same holds true of simulations in climate science, for example.[2] If a climate model is supposed to test the hypothesis that increasing concentrations of CO_2 in the atmosphere will result in an increased frequency of tropical cyclones, we do not expect the cause and effect in the simulation to be identical to the real thing, e.g., we do not expect the climate model to literally generate hurricanes. Instead, we require an appropriate analogy between the inputs and outputs of the real climate and those in the simulation. But how does one go about creating a mouse model whose inputs and outputs are human enough to serve as a simulator of human disease?

In what follows, I examine this practical problem from a conceptual perspective. My solution comes in the form of three requirements. In order to make a humanized mouse with part-human potential, one must 1) choose the right partitioning frame; 2) correctly identify part-boundaries; and 3) eliminate contextual constraints. The first two requirements ensure that the parts chosen for transfer in the human, e.g., human genes, chromosomes, cells, etc. are the ones that give rise to the target phenotype, e.g., Down

[2] Thanks to Dan Steel for this example.

syndrome. The last requirement ensures that differences between donor and recipient that could prevent transferred parts from giving rise to analogous traits in the recipient are eliminated.

The structure of the chapter is as follows. In the next three sections, I demonstrate the force of each requirement with examples from current research, and argue that if they are met, the mouse has the potential to count as part-human and serve as a simulator of human disease. In the fourth section, I consider possible objections to my argument. Finally, I conclude by showing that the scope of my requirements is not limited to humanized mice.

Partitioning Frames

The process of making humanized mice typically proceeds from donor to recipient—that is, from human donor to mouse recipient. To begin, one must identify the parts to be transferred from the donor.[3] How should the parts be chosen? It depends on how one divides an organism into parts. William Wimsatt, for example, makes use of the idea of a partitioning frame. The frame dictates which parts are relevant and which ones ought to be ignored, given some explanatory project (Wimsatt, 1972; see also Winther, 2006). Thus, on a morphological partitioning frame, the relevant parts are

[3] It might seem that the process of making humanized mice begins with modifying the recipient to prevent it from rejecting transferred parts, e.g., weakening the immune system of the mouse (see Chapter 3). While this may be the *actual* first step, it is not the first step in the design of the experiment. In order to know how to modify the recipient, one must first know what parts will be transferred.

static structures, e.g., skeletal or muscular, whereas on a physiological partitioning frame, an organism is divided into processes, e.g., immunological or digestive, and so on (Winther, 2011).

However, the partitioning frame used for making humanized mice has to be different from those above, since the relevant parts—i.e., the parts to be transferred across species—are determined by a distinctive explanatory project. If the project is to express some trait in a base population, then we must first identify all the parts that contribute to this trait in the target population. For example, if the goal is to make a mouse that can secrete lactoferrin—a human milk protein—in its milk, then the parts to be transferred should include the gene that codes for lactoferrin plus any additional regulatory regions that would ensure the protein is only expressed wherever and whenever milk protein is expressed.

Unfortunately, identifying all the relevant parts for transfer across species is not always as straightforward as this example suggests. What counts as a relevant part often depends on how the target phenotype evolved—e.g., whether or not it coevolved with some other feature of the organism. For example, the beaks of Darwin's finches on Galapagos Island probably evolved independently or at least without any obvious changes to the rest of the organism (Wagner, Pavlicev, & Cheverud, 2007). But not every feature of an organism has an evolutionary history to call its own. For instance, Gould and Lewontin (1978) argue that the human chin did not

evolve on its own but rather as a side effect of the way the jaw grows. Therefore, it should not be studied as a separate part. Sterelny and Griffiths (1999) point to a similar example in Old World monkeys: the muzzles of male Mandrills are electric blue but so are their behinds and genitals. Is each of these salient parts of the male monkey separate or are they parts of a single evolving trait?

I propose that questions of this sort—i.e., questions concerning the evolutionary history of a trait—need to be taken into consideration when making humanized mice. Why? Because knowing how the target phenotype evolved helps in identifying all the parts involved in its expression. To see the benefits of this evolutionary perspective, consider a recent experiment in which mice were genetically engineered to carry a humanized version of the Foxp2 gene (Enard et al., 2009). Commonly referred to as "the human language gene," Foxp2 gained popularity when it was identified as the cause of a severe speech and language disorder in half of the members of a large London family of four generations (Vargha-Khadem, Watkins et al. 1995). The affected family members had trouble processing and expressing grammar and their articulation of speech and nonlinguistic oral and facial movements were grossly defective. DNA analysis showed that the affected individuals carried one nonfunctional Foxp2 allele due to a heterozygous point mutation.

The human Foxp2 gene differs at only three amino acid positions from its orthologue in the mouse and at two positions from its orthologue in the chimpanzee (orthologues are genes that differ from each other as a result of speciation but are related to each other by descent from a common ancestral gene). Thus, by looking at the human Foxp2 gene and its orthologues in the mouse and the chimpanzee, we can infer that only a single amino acid substitution occurred on the mouse lineage since the evolutionary lineages leading to chimpanzees and mice diverged 70 million years ago. The hypothesis, then, is that the two substitutions that accumulated on the human lineage since the split from the chimpanzee were subject to positive selection due to their effect on language (Enard et al., 2002). Thus, in the Enard et al. (2009) experiment, the two substitutions were transferred into mice to test their effects in nonhuman organisms. The study showed that although they remained within normal range, transgenic mice with the "humanized" version squeaked at a lower frequency than wild-type mice.

Due to the frequency change in their squeak, these humanized mice made headlines around the world (cf. Wade, 2009). Did they acquire a phenotype analogous to human language? It is hard to say, since mice lack anything that we would identify as a language. Nevertheless, squeaking at a lower frequency seems far from the target. I propose that the right partitioning frame can bring us closer. Again, the right partitioning frame is simply the one that will allow us to pick out the parts that give rise to the

target phenotype, and we are more likely to choose the right partitioning frame if we consider how the target phenotype evolved. For instance, if humans share nonvoluntary vocalizations e.g., grunts, cries, screams, etc. with other animals, such as mice and chimpanzees, but they also have an unmatched ability to learn vocalization, we should inquire as to how the voluntary control of vocalization evolved.

The involvement of the Foxp2 gene in grammar and articulation in humans was discovered through a mutation. Such discoveries are obviously valuable. My point, however, is that the evolutionary history of a trait, especially a complex trait such as language, can provide insights as to where else to look and what other parts might be relevant. For example, we should ask about: 1) memory—it imposes limits on the recursive property of human language as well as the ability to form complex sentences; 2) the generation of sound—in humans it is by oscillation of vocal folds as opposed to mice who generate sound by an aerodynamic whistle; 3) motor control, e.g., the ability to learn and coordinate muscle movements in the lungs, larynx, tongue and lips—it is necessary for articulation; and 4) lung capacity—it imposes a limit on the length of spoken sentences (Hauser, Chomsky, & Tecumseh, 2002). In sum, understanding the evolutionary history of the target phenotype will help us locate all the parts that contribute to its expression.

Of course, locating all the parts required to express a given characteristic can be an overwhelming task. Luckily, however, we need not

worry about a one-to-one correspondence between parts in a base and target population; the base population is a model, and a model does not have to replicate every aspect of the target system in order to be successful. In fact, many successful models ignore variation or exclude variables present in the target system for descriptive and explanatory purposes (cf. Downes, 1992; Weisberg, 2007). For instance, a classical mechanics model of the planetary system describes the planets as only having shape and mass, disregarding all the other properties (Frigg & Hartmann, 2009) and the interior space of a cell in a biology textbook is often depicted as relatively empty even though intercellular space is known to be crowded (Love, 2010).

One strategy for choosing which elements of the target system to ignore and which to highlight in the model is to downplay the external elements with which the target system interacts, in order to narrow in on the causal interaction between the internal elements of the system (Love, 2010; see also Bechtel & Richardson, 1993). Another strategy, and the one that is well suited for simulating human disease in mice, is to focus on the parts that Kenneth Waters (2007) calls "difference-makers." Waters does not discuss difference-makers in the context of models—his focus is on genetics—but I find his concept especially useful for thinking about mouse simulators of human disease. In order to ultimately explain what it means to be a difference-maker in genetics, Waters begins with a simpler example. The example is of Mary lighting a match. Waters asks: How can we explain that it

is Mary's striking a match, rather than the presence of oxygen, that caused a match to light? According to Waters, counterfactual theories cannot provide the explanation:

> Mary's striking the match counts as a cause on counterfactual accounts because if Mary had not struck the match, then the match would not have lit. But the same reasoning leads to the conclusion that the presence of oxygen was also a cause; if oxygen had not been present, then the match would not have lit. (Waters, 2007, pp. 1-2)

Waters does not deny that oxygen is a real cause in this example. He simply believes, as most of us would, that oxygen is not what *made the difference*. The problem is that our belief that oxygen is not the difference-maker is usually based on mere intuitions. Unless, according to Waters, Mary is not holding a single match but a box of matches. If a box of matches were present, our belief would be justified because although oxygen was present, none of the other matches lit. In other words, the key to identifying causes that make a difference is having access to a multiplicity of outcomes rather than a single event. The same principle applies in the context of genetics. As Waters points out, even scientists would have no basis for thinking that the polypeptide's linear sequence is determined by DNA rather than RNA if they had only a single translation event to work with (Waters, 2007). Given a multitude of translation events, however, they could conclude that although both DNA and RNA polymerase are real causes of a polypeptide sequence, only DNA is a cause that makes a difference.

Here is why Waters's concept of a difference-maker is helpful for meeting the first requirement, i.e., choosing the right partitioning frame. It might turn out that a uniquely human environment is a necessary "part" of language acquisition and thus ought to be duplicated (if possible) in humanized mice experiments. But it might also turn out that although the right environment is necessary for language acquisition, it is nonetheless not a difference-maker. If the right environment is not a difference-maker then we should ignore it in the initial process of humanizing mice, because, on my account, the right partitioning frame will help us locate the parts that make a difference to the target phenotype and exclude parts that make no difference.

Let me wrap up this section with a brief summary. The process of making humanized mice begins with identifying the relevant parts to be transferred from the donor. In this section, I have argued that the right partitioning frame will help us locate which parts are relevant and which ones ought to be ignored, given some explanatory project. If the project is to create a mouse that can express a target phenotype, then we should take into consideration how the target phenotype evolved, and what parts *make a difference* to it, when choosing partitioning frames.

Part Boundaries

Once the parts to be transferred are identified via the right partitioning frame, the next step is to isolate them from a complex system.

According to William Bechtel and Robert Richardson (1993), there are three types of complex systems: *aggregative*, *component,* and *integrative*. Each type corresponds to a unique way in which the parts of the system contribute to its performance. The contribution of the parts to the system's performance determines the suitability of decomposition as an investigative strategy. For example, an *aggregative* system is completely decomposable into parts because its components simply add together, i.e., they make independent contributions to the performance of the system (Wimsatt, 1972). In contrast, a *component* system is nearly decomposable because its components retain their own integrity but make contributions to the performance of the system by interacting sequentially or linearly with other components. In contrast to both of these, an *integrative* system is minimally decomposable because its components interact with each other in nonadditive ways and are integrated to such a degree that their organization, rather than their distinctive properties, is more important to explaining the performance of the system (Bechtel & Richardson, 1993; see also Haugeland, 1998; Kauffman, 1971; Simon, 1969; Wimsatt, 1972). Organisms tend to fall into this last category. Their parts are not functionally independent, nor do they contribute to the behavior of the organism in a linear way. Rather, they are mutually dependent on other parts that may be located outside of their compartmental boundaries.

For example, some parts of the brain transgress compartmental boundaries. In his recent book, Carl Craver (2007) identifies the action potential in the brain as that kind of part:

> The mechanism of the action potential relies crucially on the fact that some components of the mechanism are inside the membrane and some are outside. The membrane allows the intracellular and extracellular concentrations of ions to be different, allows a diffusion gradient to be set up, and allows for a separation of charge. (Craver, 2007, p. 141)

Some parts of a minimally decomposable system interact not only with things outside of their compartmental boundaries, like the action potential in the brain, but also with things outside of the organism. For example, an organism's part may be homeostatic and self-regulating in response to environmental changes (Bechtel & Richardson, 1993). Plants are minimally decomposable in this way since the height of a plant can depend on the interaction of various parts within its cells as well as the interaction between the plant and its environment (Lewontin, 2002).

To see the logistics involved with identifying the relevant parts for transfer out of a minimally decomposable system, consider the O'Doherty et al. (2005) mouse model of Down syndrome (DS). DS is a human genetic disorder caused by an extra copy of chromosome number 21. Thus, O'Doherty et al. inserted human chromosome 21 into mice with the hope of modeling the disorder in rodents. The mice were tested for various symptoms of DS, which typically include mental retardation along with craniofacial abnormalities, brain volume reduction and congenital heart defects. To check for mental

retardation, experimenters conducted behavioral, learning and memory tests. The mice showed a trend toward hyperactivity compared with wild-type littermates, although the trend did not reach significance. Moreover, the mice seemed capable of retaining short-term memory for up to a minute but were deficient in long-term memory. The density of neurons was significantly lower in the cerebellum of DS mice than wild-type littermates, ~60% of DS mice had congenital heart defects compared to ~40% in humans with DS, and DS mice had a small mandible but no overall diminution in cranium size.

Given the mixed results, it is worth checking whether my second requirement was met in this experiment—i.e., whether the boundaries of transferred parts were correctly identified. The aim of the study was to model human DS in mice. In humans, cells typically contain 23 pairs of chromosomes but the cells of a person with DS contain three rather than two copies of the 21st chromosome. Thus, it appears that it is not the chromosome itself that is responsible for the illness but rather its relation to the other two chromosomes. But since mice have only 20 pairs of chromosomes, creating a mouse model of human DS by adding a third copy of mouse chromosome 21 was not an option. Therefore, O'Doherty et al. reasoned in the following way: the genes on mouse chromosome 16 have orthologues on human chromosome 21 but also on 3, 16 and 22. Consequently, adding a third mouse chromosome 16 is equivalent to adding a third copy of parts of four human chromosomes. In addition, approximately 2/3 of known genes on human chromosome 21

have orthologues on mouse chromosome 16 and the remaining 1/3 of the genes have orthologues on mouse chromosomes 10 and 17. A mouse with an inserted human chromosome 21 would thereby carry three copies of genes on that chromosome, via the existing orthologues in the mouse, while no other mouse genes would be tripled (O'Doherty et al., 2005). Since human DS seems to be caused by too many copies of a particular chromosome, the "boundaries" of the transferred parts in this experiment had to extend far enough to cover the phenomenon of excess chromosomes. Hence, the only way that the genes on human chromosome 21 could be tripled in these humanized mice was if the existing mouse orthologues were sufficiently similar to their human counterparts to count as their third copy.

However, we should wonder if this assumption was justified. Orthologues can be similar as a consequence of being related to each other by descent from a common ancestral gene. But they can also be very different, as a result of speciation. Thus, to label two genes orthologues is to make a claim about their relation to one another—not about their resemblance. Since O'Doherty et al. do not discuss the similarities between the mouse and human orthologues in their article it is possible that the genes on human chromosome 21 were not tripled in these humanized mice. On the other hand, what O'Doherty et al. did well was insert an entire chromosome—rather than individual genes—thereby compensating for the fact that genes may extend beyond their protein-coding sequences. In fact, the changing definition of a

gene and its borders provides a perfect example of what it takes to meet my second requirement.

On the classical view, genes on chromosomes were like beads on a string, each one a unit of hereditary information coding for a single protein. This definition has changed dramatically in the last twenty years, especially post-ENCODE. The aim of the ENCODE project was to characterize 1% of the human genome using various experimental and computational techniques. The picture that emerged is extremely complex (Gerstein et al., 2007). As Falk (1986) predicted, the gene is neither discrete, nor continuous, nor has a constant location, function, sequence or definite borders. Given the complex nature of the gene, by inserting an entire chromosome, O'Doherty et al. increased the likelihood that all the genes on that chromosome—whatever their borders and location—would also be transferred.

What we see then is that locating the boundaries of human parts to be transferred into a mouse—with the aim of simulating a human disorder—is a difficult task. Animals are integrative systems. The fact that they are not easily decomposable into parts can pose problems. Indeed, the less decomposable the donor and the recipient, the harder it is to correctly identify the boundaries of parts to be transferred, and the less likely that the transferred parts will give rise to an analogous human phenotype in the mouse recipient.

Contextual Constraints

The act of choosing the right partitioning frame and isolating parts for transfer happens prior to transplantation. Once the parts are isolated, they are inserted into the recipient where they are expected to give rise to the target phenotype. This expectation arises from a tendency to think of parts as entities whose properties can be examined and defined in isolation from the whole, and a tendency to think that parts will preserve their properties even after they have been transplanted into a new location. Human to human kidney transplants support this line of thought: the properties of the kidney are the same before and after transplant. But as Richard Lewontin and Richard Levins point out (2007), the concepts of "part" and "whole" are reciprocally related: Something cannot be a whole unless there are parts that make it up and conversely, nothing can be a part unless there is a whole of which it is a part, "parts do not come together to make wholes but come into being in them only as the whole comes into being" (Lewontin & Levins, 2007, p. 132).

Consider the mitochondrion as an example of this reciprocal relationship. The mitochondrion is an organelle found in most eukaryotic cells. Its primary function is to supply cellular energy but it is also involved with other processes—e.g., signaling, cellular differentiation, control of cell growth, etc. What is interesting about the mitochondrion from the evolutionary perspective, however, is that it contains its own DNA, which is

circular like that of bacteria. In addition, it is similar to bacteria in that it has its own machinery to transcribe and translate that DNA, has an outer membrane, and divides by fission—rather than by mitosis like the other organelles. These and other observations led to the endosymbiotic hypothesis for the origin of mitochondria (Margulis, 1970). The hypothesis states that single-celled organisms captured smaller organisms, e.g., bacteria, and used them as an efficient source of energy via endosymbiosis. Eventually, bacteria simply became mitochondria.

Today the mitochondrion is a part in a cell, but even if it could survive outside of it (given its evolutionary past) isolating it from the cell would not be a fruitful way of getting at its current properties. The properties of the mitochondrion, as a part, manifest themselves in its incorporation and integration in the cell (Bechtel & Richardson, 1993). The same holds true for many biological parts, e.g., genes and cells. Their properties become manifest when they are part of a living system and these properties can change when the properties of the living system change.[4] Given this fact, when making humanized mice we must ask whether the transferred parts—even if identified correctly—can give rise to the same phenotype in the context of a different species. In the remainder of this section, I argue that biological differences between human and nonhuman organisms can act as phenotypic constraints and regulate what can and cannot become of transferred parts in

[4] The exception are parts of organisms which are integrated into the organism but are at the same time relatively autonomous with respect to other parts of the organism, i.e., modules (cf. Wagner, Pavlicev, & Cheverud, 2007)

a new context. In other words, species differences must be considered when trying to extrapolate across species boundaries.

It might be helpful to illustrate the importance of such considerations with an example. James et al. (2006) attempted to make human-nonhuman chimeras by dissecting 6-day-old human embryos into clumps of cells and injecting those cells into 3.5-day-old mouse embryos. Thus, both the transferred cells and the cells of the host were ES cells. The chimeric blastocysts were transferred into the uteri of pseudopregnant mice. At embryonic day 8.5, James et al. terminated the pregnancies of these mice. The embryos were then examined for human ES cell contribution. The results showed that only 4 out of the 28 chimeric embryos that were implanted contained human ES cell derivatives and 3 out of the 4 were developmentally abnormal. Only one embryo was morphologically similar to normal littermates and contained ten human ES cell derivatives (James et al., 2006). What happened to all of the other human ES cells? And why did most of the embryos that still had some, develop abnormally?

The answers to these questions are probably tied to the differences in rate of development between the two species. In contrast to humans, who are pregnant for 9 1/2 months, mice are pregnant for a mere 20 days. Due to the longer gestation period, human ES cells grow at a slower pace than mouse ES cells and are thereby likely to be outcompeted by mouse cells in a blastocyst-stage chimera. Stages of development, relative to the gestation period of each

species, also differ. In humans, for example, eyelids open on the 7th month of fetal life but in the mouse, eyelids remain closed until 12-14 days after birth (Kaufman, 2007). Moreover, mice and humans have significant differences in the signaling factors that mediate cell self-renewal and senescence. In humans, the clock that keeps track of cell divisions and signals cell cycle arrest is the telomere. It shortens as the cells divide. In mice, however, the telomeres are significantly longer at all stages of cell development making it unlikely that they undergo telomerase-based senescence (Kipling & Cooke, 1990).

In addition, there are differences in size, lifespan, and evolutionary history between mice and humans—factors especially relevant for modeling human disease. Humans are 3,000 times larger than mice. The increase in cell number corresponds to 10^5 more mitoses. Moreover, processes such as mutation repair and stress response differ in humans whose life expectancy is ~70 years, compared to 2 years in mice, and our longer lifespan means an increased risk in generating cancerous mutations (Beckers, Wurst, & Hrabé de Angelis, 2009). In addition, the two species evolved in different ecological niches with different pathogens (Hughes & Mestas, 2007). Not surprisingly, then, mice and humans have different immune systems. For example, their respective cells of the immune system—e.g., T and B cells—tend to reject tissue transfers from the other species, e.g., a skin graft from a human will be

rejected by the mouse and vice versa.[5] Mice also lack a peripheral immune system present in humans, composed of lymph nodes, thymic tissue and Payer's patches. Cytokine molecules, secreted by immune cells to signal other immune cells, are species specific as well.

These differences help explain why therapies that work on mice often fail to provide similar results in our own species (Hughes & Mestas, 2007; see also Monaco, 2003; Oehler & Bicknell, 2000; Panitch, Hirsch, Haley, & Johnson, 1987; Shepherd & Sridhar, 2003; Sykes, 2001; van Oosten et al., 1996; Wood, 2003). Although contextual differences tend to narrow when species are closely related, the relation between the species has to be intimate for this to happen. Chimeras generated from mixing embryos of *M. musculus* and *M. caroli* (mice) developed successfully to adulthood, but chimeras between mouse and vole and mouse and rat did not come to term (James et al., 2006), presumably due to the irreconcilable differences I outlined above. However, the important point is that although some differences between humans and mice can be overlooked in humanized mice experiments, the ones that act as contextual constraints on the target phenotype cannot.

Given the vast number of these constraints, it is hard to believe that transferred human cells *can* proliferate in the context of a mouse. While this does happen, the extent to which these cells are still "human"—except by origin—is debatable. Another example helps us see this point: The

[5] The aim of creating immunodeficient mice is to eliminate some of these differences (see Chapter 3).

experiment by Muotri et al. (2005) in which 10^5 human ES cells were injected into the brains of 14-day-old mouse embryos. The stages of development were mismatched in this experiment: the embryos were advanced enough to have a developing brain—day-14 relative to the 20-day-long gestation period in mice—while the injected undifferentiated cells were derived from human blastocysts. The embryos were removed with intact placentas from pregnant females and placed back after injection. Pups were born by normal vaginal delivery. The results showed that only < 0.1% of the brain cells in the mice were of human origin. However, there was widespread incorporation of human ES cells in a variety of regions: cortex, hippocampus, thalamus, striatum and corpus collosum. What is interesting is that the cells that integrated into the host tissue had dimensions similar to those of adjacent cells—their size, shape and orientation adjusted to the preexisting cellular architecture. For example, the diameter, orientation and branching patterns of human ES cell derived neurons, astrocytes and oligodendrocytes were indistinguishable from those of their host counterparts. In addition, transplanted cells seemed to regulate their maturation speed and size and establish contact with host neurons within the recipient's granular layer of the hippocampus. This indicates remarkable adjustment to the new environment since in humans, granule cells in the hippocampus are not formed until 4 to 6 months *after* birth (Muotri, Nakashima, Toni, Sandler, & Gage, 2005).

The fact that transferred human cells proliferated in this experiment might be perceived as evidence against my third requirement—that contextual constraints must be eliminated. After all, the differences between mice and humans that I emphasized above were not an obstacle to these transferred cells—the cells multiplied, migrated, and integrated into the host organism without complications. But in what sense, except by origin, were these cells still human? Not only were they indistinguishable from their host counterparts, in terms of size, shape, orientation, etc., but their rate of development adjusted to that found in the mouse. As a result, it is more reasonable to interpret the human cells mimicking the mouse cells as a vindication of my third requirement. What it shows is that the context of the host organism can be powerful enough to force human ES cells to behave like mouse cells. If transferred human cells start behaving like mouse cells, then they are unlikely to give rise to whatever human phenotype they were expected to give rise to.

Objections Considered

Before wrapping things up, I want to consider an important potential objection to my argument. Someone might think that my requirements are too formulaic and that they consequently fail to account for the array of complexities found in nature. When we study complex adaptations, for example, it often turns out that the "one structure—one function"

relationship does not hold; the same structure may lead to different functions and different structures may lead to the same function.

For example, in genetics the ability of structurally different elements to "perform the same function or yield the same output" (Edelman & Gally, 2001, p. 13763) is known as *degeneracy*. When scientists knock out selected genes through homologous recombination, the expected result is a phenotypic effect that can be attributed to gene loss—sometimes an effect that ultimately leads to the death of the organism. But in up to 30% of the cases, there is no effect on the phenotype despite the absence of the gene product. "Some examples include mice that are unable to make such seemingly important proteins as myoglobin, tenascin C, vimentin, gelsolin, and a neurofilament subunit" (Edelman & Gally, 2001, p. 13763). In these mice, the absence of the above gene products has little or no effect on their phenotypes. The proposed explanation for these findings is "that the gene networks of the affected animals are degenerate, allowing widespread, compensatory adjustments" (Edelman & Gally, 2001, p. 13763).

The fact that target phenotypes can be multiply realized is, indeed, a potential problem for my requirements. One might expect my first requirement—choosing the right partitioning frame—to account for degeneracy. For instance, recall the mouse that can secrete a human protein in its milk. One might expect the relevant parts chosen for transfer to not only include the lactoferrin gene (plus some regulatory regions), but also

other elements that may compensate for the possible loss of this gene in humans. Let me put this objection in broader terms: we expect of a simulation to not only mimic the target when the target functions properly but also when it malfunctions. However, there are a couple of problems with this expectation, at least as it applies to degeneracy. First, we simply may not know all the parts that are involved in degeneracy, and second, including all such elements might make the task of identifying the relevant parts for transfer too complicated. Both problems are legitimate but neither one undermines my project. My requirements are meant to provide *idealized* sufficient conditions for making a mouse simulator of human disease. Hence, the content I provided under each requirement is not meant to be exhaustive. What it means to choose the right partitioning frame may be adjusted as scientists come across new findings, such as all the parts involved in degeneracy.

Conclusion

Establishing what it means to be human, or part-human, in the age of advancing biotechnology, is a difficult task. In this chapter, I have argued that if certain requirements are met in the process of making humanized mice—1) if the right partitioning frame is chosen, 2) if the part boundaries are correctly identified, and 3) if contextual constraints are eliminated—then

humanized mice have the potential to count as part-human. Otherwise, they are merely partially composed of human parts.

In closing, I want to point out that the scope of my requirements is not limited to humanized mice. Whenever biological parts are transferred from one living entity to another with the hope of producing some target phenotype, my requirements apply. In fact, they help predict which experiments will succeed and explain why they do. For example, consider human to human kidney transplants. My requirements explain why such experiments are successful: first, since both the donor and the recipient are of the same species, it is easy to choose the right partitioning frame; second, the boundaries of a kidney, as an organ, are easy to pick out; finally, most contextual constraints are avoided. The only significant contextual constraint is the immune system, but immunosuppressant drugs can be prescribed to prevent rejection of the organ. In sum, human to human kidney transplants are successful because they meet the three requirements I have proposed in this chapter. Of course, if human-to-human kidney transplants are our best success story, then transplanting human parts into mice with the hope of creating a part-human simulator of human disease will be quite challenging.

CHAPTER 6

THE MORAL STATUS OF PART-HUMANS

A number of years ago, Irving Weissman, a professor at Stanford University, had an idea for an experiment: Make a mouse whose brain is made up of human neurons. This mouse would be an interspecies chimera since it would contain cell populations derived from at least two different zygotes of different species (see Chapter 3). To make the human neuron mouse, Weismann decided to use a line of mice from Harvard University because their neurons die a week before birth, which normally leads to the death of the mouse as well (Scott, 2006). But rather than let these neuron mice die, Weissman wanted to see if by transplanting human neural stem cells *in utero*, mice with brains repopulated by human neurons could survive. Before conducting the experiment, Weissman asked a panel of Stanford bioethicists and scientists to evaluate his proposal. A number of ethical issues were discussed in the panel's published findings, but the possibility of conferring humanity onto a mouse, and thereby the moral status that goes

along with being human, has received significantly more attention than the other issues.

In response to these findings, Mark Sagoff (2007) has argued that conferring humanity onto a mouse cannot be a real moral concern, since no one seems to be troubled by the fact that many animals already have human characteristics. According to Sagoff, what is really troubling the ethicists is that the cells present in the mouse are derived from *Homo sapiens*:

> What makes the activity of the neuron mouse *human* is not its content or character—there may be animals, such as dolphins, that apparently act the same way—but its association with the introduction of cells taken from *Homo sapiens*. What if the introduction of dolphin brain stem cells into fetal mice produced similar or even more "human-like" results? Would the moral problem disappear or be different? (Sagoff, 2007, pp. 51-2)

Sagoff leaves these questions unanswered, but the rest of the article implies that he thinks mice should be judged based on their characteristics rather than on the types of cells, e.g., human or dolphin, that gave rise to particular characteristics.

In the previous chapters I emphasized the importance of establishing the relative humanness of part-humans for the sake of ethical and legal regulations based on the human/nonhuman distinction. Yet, there are many ethicists like Sagoff who are against giving preferential treatment to humans over nonhumans. Opponents of the human/nonhuman distinction instead tend to favor the person/nonperson distinction (or some version of it). According to this way of seeing things, a person is someone with

characteristics that we believe to be morally relevant, e.g., the ability to feel pain, the ability to reason, etc. and insofar as one has these characteristics, one can be a *person* even if one is not *human*. Given this distinction, it may seem that a proponent of the personhood view will find the humanness of part-humans irrelevant to how we ought to judge their moral status. After all, if being human does not matter for being a person, why care about how human something is? But this is precisely the problem Sagoff is raising. Is the causal history of an acquired characteristic, e.g., whether that characteristic came about as a result of a dolphin or a human transplant, morally irrelevant to the status of that creature? This is the question on which I want to focus in this chapter. In the first half, I argue that causal history is morally irrelevant to the *ontological* moral status of the animal. Conversely, the second half argues that causal history is *epistemically* relevant to our ability to detect that moral status. The goal then is to establish what the appropriate role of causal history is in judgments of moral status, especially as they apply to part-humans.

The Ethical Debate

The distinctive concern about part-human research, according to Greely et al., is that the transfer of human parts might confer human moral status onto nonhuman organisms:

> What we called "conferring humanity on mice" seems to be the main concern in the literature on chimeras…the authors have

> not used our language of "conferring humanity" on the transplanted animal, but the concerns each expresses seem equivalent to the concerns we encompassed in our term. (Greely et al., 2007, p. 36)

Greely et al. discuss the idea of transferring humanness onto mice and ask whether part-human experiments could transform a mouse into a man, "or to be more precise, into a creature with some aspects of human consciousness or some distinctively human cognitive abilities" (Greely et al., 2007, p. 35), perhaps in the way that Gregor Samsa, a character in Kafka's *Metamorphosis*, was transformed into a cockroach.

The other authors who worry about conferring humanity onto nonhuman organisms include Karpowicz et al. They warn against part-human research, especially "if human-like capacities associated with human dignity were to emerge in such animals to some degree" (Karpowicz, Cohen, & Van Der Kooy, 2005, p. 124). Their argument proceeds as follows. If human dignity is an unconditioned worth unique to humans, then the transfer of human components might confer human dignity upon an organism that previously lacked such dignity. But placing components necessary for human dignity into a nonhuman body where they cannot function fully, if at all, would diminish or eliminate human dignity.[1] Robert Streiffer (2009) thinks

[1] Although Karpowicz et al. attempt to ground human dignity in "a *cluster of capacities* that matter ethically and that members of that species generally exhibit" (Karpowicz, Cohen, & Van Der Kooy, 2005, p. 121, emphasis mine) they also ascribe human dignity to all humans no matter how seriously impaired they may be, "those who are human and yet display a limited subset of these capacities, say, the newborn infant or the person with severe disabilities, still have human dignity" (Karpowicz, Cohen, & Van Der Kooy, 2005, p. 121). As Streiffer rightly points out (2009), these answers are inconsistent. It cannot be the case that

this argument is a nonstarter because it generates the following dilemma. On the one hand, if the introduction of human components confers human dignity onto an organism that previously lacked such dignity, then the research does not diminish or eliminate human dignity but rather enhances it. On the other hand, if the introduction of human components does not confer human dignity onto an organism that otherwise lacked such dignity, then, again, the research does not diminish or eliminate human dignity, since that dignity was never there to begin with (Streiffer, 2009).

Instead, Streiffer argues that enhancing the moral status of an organism is *prima facie* good. The problem, rather, is "that the subsequent treatment of the subject likely will fall far below what its new moral status demands" (Streiffer, 2005, p. 348). If the transfer of human parts into an organism can enhance its comparatively low moral status to that of a normal human adult, then we ought to treat that individual as we treat others with full moral status. However, if we continue to treat that individual as we treat other nonhuman organisms in a laboratory setting, then "what would have been animal confinement, pain, suffering, and death, becomes the moral equivalent of…human confinement, pain, suffering, and death" (Streiffer,

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some capacities determine whether an individual has human dignity and at the same time that all humans have human dignity and no nonhumans have it. Seeing that "capacities" are not actually doing any of the work for Karpowicz et al., I omitted them in my reconstruction of their argument.

2009, p. 34). This makes status-enhancing research much worse than research on nonhuman organisms, according to Streiffer.

Finally, Baylis and Robert also focus on the possibility of conferring humanity onto nonhuman organisms. Their worry, in contrast to the worry of Streiffer and Karpowicz et al., is that part-human research might create confusion about the moral status of the animals, "The engineering of creatures that are part human and part nonhuman animal is objectionable because the existence of such beings would introduce inexorable moral confusion in our existing relationships with nonhuman animals" (Robert & Baylis, 2003, p. 9). Here is a short recapitulation of their argument, which they do not endorse but note as the strongest argument against part-human research. If an individual is a human being, it has full moral status. If it is not human, its moral status is contingent upon the attitudes of its human creators or overseers. This is evident in our thinking about rights to life, for example. A nonhuman animal's right to life depends on the will of human beings while human beings have a right to life simply in virtue of being human. This conclusion implies a strong dichotomy between the moral status of humans as opposed to nonhuman animals, and the fact that part-humans are neither fully human nor fully nonhuman generates confusion regarding the ethical treatment of part-human organisms (Robert & Baylis, 2003). In sum, the ethicists who write on the topic of part-human organisms tend to worry (or recognize the worry) that biological humanization of nonhuman

organisms might lead to their moral humanization. To avoid this morally problematic result, they suggest various restrictions on part-human research.

The Personhood View of Moral Status

What is at stake in the above mentioned debate is the moral status, or moral standing, of part-humans. Analogous to legal standing—which gives one the right to bring one's claims before a court—moral standing gives one the right to have one's interests taken into account as morally good reasons to be treated in this way or that (Rachels, 2004). The belief that moral standing runs along species lines, i.e., that human beings have the moral status they do because they belong to the species *Homo sapiens*, is known as *moral anthropocentrism*. The views of the ethicists I outlined above are morally anthropocentric, although the authors may have different motivations for subscribing to such a view. Streiffer (2010), for example, is explicit about the pragmatic advantage of subscribing to it, since most people within the scientific and medical communities also subscribe to it. Regardless of the motivation, it is clear that Sagoff is right—the ethicists in this debate are of the opinion that inserting cells or genes derived from *Homo sapiens* into nonhuman organisms is likely to affect their moral status.

The most famous criticism of moral anthropocentrism comes from Peter Singer (1975). According to Singer, discriminating among individuals on the basis of species membership alone makes one a "speciesist," analogous

to a sexist who discriminates among individuals on the basis of sex membership. While there are biological differences between species and sexes, these differences are not *morally significant* ones, according to Singer. That's why speciesism and sexism are forms of arbitrary discrimination. Which differences are the morally significant ones? Many ethicists think that it is the mental characteristics of an individual that make the moral difference. Since not all human beings have the relevant mental characteristics, and since some nonhumans might have them, moral boundaries are not co-extensive with species boundaries. Cora Diamond summarizes this view as follows:

> If (for example) we treat as the properties which make us human the capacities for reasoning and self-consciousness, then indeed these capacities may be morally relevant, but if they are morally relevant at all, they are significant whether they are the properties of a being who is a member of our species or not. And so it would be better to use a word like 'person' to mean *a being that has these properties*, to bring out the fact that not all human beings have them and that non-human beings conceivably have them. (Diamond, 1991, p. 35)

As Diamond points out, the term 'person' may be used for individuals who possess morally relevant characteristics and this term may refer to humans and nonhumans alike. For example, John Locke uses the term 'person' interchangeably with 'moral Man' and defines it as a "forensic term, appropriating actions and their merit" (Locke, Essays II xxxvii, p. 26). For Locke, a monkey that has the ability to reason would also count as a person:

> For were there a Monkey, or any other creature to be found, that had the use of Reason, to such a degree, as to be able to understand general Signs, and to deduce Consequences about general *Ideas*, he would no doubt be subject to Law, and in that Sense, be a *Man*, how much soever he differ'd in Shape from others of that Name. (Locke, Essays III, xi, p. 16)

On the other hand, Immanuel Kant thought that personhood did not turn exclusively on the capacity to reason, but also required that an individual be autonomous. In virtue of having these capacities, persons are free to determine themselves "as ends in themselves," while nonpersons are beings whose ends are determined by others (Kant, 1964). It is because persons are rational and free that they are capable of being blamed, praised and held responsible for their actions. Harry Frankfurt adds an additional requirement: A person is someone who is capable of forming "second-order desires" (Frankfurt, 1971). A second order-desire is a desire about a desire. For example, an addict's desire for a drug is a first-order desire. The addict is engaged in the conscious activity of desiring the drug but he is not conscious *of* his desire. His desire is not the object of his attention—he does not think *about* it (Korsgaard, 1996). In contrast, a recovering drug addict not only desires a drug but also desires not to desire the drug. This is a desire of the second order.

For utilitarians, like Singer, who value the promotion of happiness and the avoidance of pain over anything else, the mental characteristic relevant for moral status is sentience (or the ability to feel pleasure or pain). Jeremy

Bentham was the first utilitarian to write about the importance of sentience for moral status:

> It may come one day to be recognized, that the number of legs, the villosity of the skin, or the termination of the os sacrum, are reasons equally insufficient for abandoning a sensitive being to the same fate. What else is it that should trace the insuperable line? Is it the faculty of reason, or perhaps, the faculty of discourse?...the question is not, Can they *reason*? Nor, Can they *talk*? But, Can they *suffer*? (Bentham, 1879, p. 311)

According to Bentham, there is no justifiable way of excluding individuals from the moral community if they have the capacity to suffer. Similarly, Singer maintains that the comparable interests of all sentient beings be given equal weight independent of whose interests they are and what other qualities they may possess. Hence, my own interests should not count more than the interests of anyone else and neither should the interests of my own species. Singer's reasoning here is based on the concept of equality—not as a statement of fact but as a moral idea about how we ought to treat one another. "The principle of the equality of human beings is not a description of an alleged actual equality among humans: it is a prescription of how we should treat human beings" (Singer, 1989, p. 165). For Singer, the concept of equality applies to all species. The fact that some animals are less intelligent than others does not mean that their interests should be disregarded.[2] If they

[2] Although Singer argues that psychological capacities, such as intelligence, do not undermine the interests of an individual, VanDeVeer points out that weighing the interests of beings with more complex psychological capacities more heavily than those without such capacities is not incompatible with Singer's position. Humans can suffer from the dread of impending disaster, e.g., death from cancer, in a way that other animals cannot, "a turkey

are sentient, then they have interests, and those interests warrant equal consideration (Singer, 1979).

Singer's commitment to the equality of sentient beings is an answer to the question "How should we treat one another?" Following James Rachels (2004), I take it that the reason there is disagreement among philosophers about which mental characteristics are required for personhood is because the answer depends on the moral question. For example, if the question is about moral responsibility, a relevant mental capacity might be the ability to reason. After all, we do not hold someone morally accountable unless that individual has the ability to recognize the difference between right and wrong. If the question is about who we should or should not torture, on the other hand, a relevant mental capacity is likely to be sentience. If the question is about who we should or should not coerce, it probably matters whether or not the individual is autonomous, and so on (Rachels, 2004). The point is that since not all human beings have this or that mental capacity, and perhaps some nonhumans also have it, the moral boundaries are not synonymous with species boundaries. Moreover, even if it turned out that all

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will not be wary of impending Thanksgiving events" (VanDeVeer, 1979, pp. 70-71). In examples of this kind, it is the difference in psychological capacities that accounts for the discrepancy in suffering. Moreover, suffering can be affected by life span and the capacity to remember, "a steer does not suffer from the memory [of being castrated] in the way that women continue to suffer from the trauma of rape, e.g., 'reliving' of the experience in dreams, and so on" (VanDeVeer, 1979, pp. 70-71). In sum, whether or not there will be long term harm is a function of the psychological capacities of the individual involved, and for that reason on Singer's account, psychological capacities (along with sentience) may play a role in how we treat one another.

and only humans were autonomous, this would be a biological and thereby a contingent fact about us—not a necessary part of being human (Kadlac, 2009).

Before I move on to the next section, I want to point out that a proponent of the personhood view of moral status need not believe that only modifications to the brain, as opposed to other parts of the body, can change someone's moral status. In their recent book, Rolf Pfeifer and Josh Bongard (2006; see also Johnson, 1990) argue that thoughts—including spatial and social cognition, problem solving, reasoning, and natural language—are highly constrained and shaped by our bodies. "The kinds of thoughts that we can produce or carry out ultimately have their foundation in our embodiment" (Pfeifer & Bongard, 2006, p. 2). Here is a brief overview of their argument. One of the most elementary capacities of any creature is categorization, or the ability to make distinctions in the world. If we cannot distinguish food from nonfood, dangerous from safe objects, our parents from other people, or our home from the rest of the world, we are not going to survive for very long. The formation of such categories is very directly determined by our embodiment, i.e., by the shape of the body, the kinds of limbs and where they are attached, the kinds of sensors (eyes, ears, nose, skin and mouth) and where on the body they are found. When we interact with the world, the body is stimulated in very particular ways and this stimulation provides the raw material with which the brain works. Even

abstract categories, e.g., mathematical notions, are influenced by our morphology. Here, the authors draw on the work of others to argue that the concepts of a real number, a set, etc., are based on metaphors (e.g., a point "moving" toward infinity) and these metaphors are, in turn, grounded in our bodies.

Pfeifer's and Bongard's argument undermines the idea that for a proponent of the personhood view, only modifications of the brain could have moral consequence. If reason is a morally significant capacity, and the way we reason is shaped by our bodies, then modification of the rest of the body could also have consequences for the moral status of an individual.

Argument Against Causal Histories Making a Moral Difference

Sagoff's view—that part-human candidates should be judged solely on their characteristics rather than on the origin of the genes or cells that gave rise to those characteristics—is consistent with the personhood view of moral standing I outlined in the last section. Put slightly differently, what Sagoff is suggesting does not constitute a controversial position among ethicists. Nevertheless, it is worth wondering why anyone would think that causal histories make a moral difference. So when do we care about causal histories? And what would embracing such a view look like?

Imagine a scenario in which one mouse fetus receives a stem-cell transplant from a dolphin and another mouse fetus receives a stem-cell

transplant from a human. Now, imagine that both of the mice acquire some new characteristic as a result of the transplant and that the new characteristics of the two mice are identical to each other. For example, they can both reason. Given the idea that causal histories make a moral difference, the fact that one characteristic came about as a result of a dolphin transplant but that the other capacity came about as a result of a human transplant *can* make a difference as to how we ought to judge the moral status of each mouse, even though the acquired characteristics are exactly the same.

This seems counterintuitive. So why would anyone hold such a view? Well, as it turns out, judging identical characteristics differently in virtue of their distinctive causal histories is fairly common in disciplines outside of the moral domain. Consider a few examples. First, artistic replicas of famous paintings are done with such precision—some even during the same time period as the original—that there is no method available to tell them apart. Yet only one of the paintings is worth a fortune—not because of any difference in their characteristics, since the two are exactly alike, but because of who painted it. Second, in medicine, illnesses are often categorized according to their causes, i.e., the etiology of the illness. Migraine headaches, for example, may be caused by vasospasm of cerebral arteries or by vasoconstriction of the innervated vascular system. Each mechanism can lead to the aura experienced during a migraine, but knowing the etiology of

migraines is critical for their cure and prevention. Third, geological history is important for distinguishing lithological properties. Basalt and Troctolite are two kinds of igneous rocks that can look exactly identical. Usually, geologists can tell the two rocks apart by their crystal size: Basalt has smaller crystals than Troctolite, because it tends to cool faster. But on occasion, the two rocks can cool at exactly the same rate and thus have exactly the same crystal size. Moreover, both rocks are abundant in olivine and plagioclase, which means that looking at their mineral composition will not help make the distinction. In such a scenario, the causal history of the rocks is the only way by which geologists can tell them apart.[3] Fourth, in cognitive ethology, the causal mechanism behind the same trait observed in two different species can affect how the trait will be categorized:

> The naturalist who studies animals in their natural surroundings must resort to other methods. His main source of inspiration is comparison. Through comparison he notices both similarities between species and differences between them. Either of these can be due to one of two sources. *Similarity* can be due to affinity, to common descent; or it can be due to convergent evolution. (Tinbergen, 1963, p. 421)

Distantly related species subject to similar selection pressures may end up with traits that are more alike than the traits of closely related species that had dissimilar selection pressures. For example, cognitive and behavioral abilities that were once considered exclusively human have been noted across some of our more distant relatives, e.g., imitation skills in domestic dogs

[3] Thanks to Matt Mosdell for this example.

(Kaminski, Call, & Fischer, 2004; Range, Viranyi, & Huber, 2007), category formation in African gray parrots (Pepperberg & Wilcox, 2000), as well as tool manufacture and use by New Caledonian crows (Chappell & Kacelnik, 2002). Whether these traits are produced by mechanisms similar to the ones found in humans, mechanisms that may have come about as a result of similar selection pressures, for example, will influence how these traits are to be categorized.[4] Fifth, and finally, in the courtroom, the causal history behind identical outcomes is critical for determining the severity of each crime, e.g., a premeditated crime is considered more severe than, say, manslaughter.

What these examples illustrate is that judging identical characteristics by their causal histories is practiced across disciplines. Of course, this might be a peculiarity of disciplines operating outside of the moral domain. Thus, in order to really see if the view has any merit, we need an example where two characteristics are identical but where differences in causal history make a difference to our *moral* judgment of each. Michael Thompson's account of "life forms" and John Searle's account of "intentionality" are the right kinds of examples. What I am going to do next is show why Thompson and Searle think that causal history should influence our moral judgment. Once I have done that, I will argue that their arguments are unconvincing.

[4] Tinbergen (1963) thought that a comprehensive categorization of a given behavior required knowledge of three additional causes: 1) ontogeny (or development); 2) adaptive significance (or adaptive function); and 3) phylogeny (or evolutionary history).

Michael Thompson's Argument for Causal

Histories Making a Moral Difference

Thompson sets out to compare the characteristics of species, or "life forms," in order to draw some normative conclusions about them. To avoid the objection that "life form" is not a category from which one can derive an "ought"—since it is a biological rather than a normative category—Thompson argues that life form is not a biological category, "The concept life form is a pure or a priori, perhaps a logical, concept" (Thompson, 2004, p. 11). Contrary to popular empiricist opinion, Thompson argues that the concept of a life form, e.g., human, is not observation-dependent. His argument for this claim comes in the form of examples. The examples are designed to illustrate the limits of empiricism—that is, to show that the way we reason about life forms goes beyond mere observation.

The first example is about umbrella jellies. Thompson asks us to imagine a scientist studying this particular life form, making various observations about it as she comes across more and more samples. She then begins to form judgments about the umbrella jelly, the kind of judgments we might hear on a nature documentary show. "The umbrella jellies have 144 tentacles" she tells us. But while our scientist has studied the life form through observation, her judgments about it are not a synopsis of what she saw. They are not about "what is always or mostly or even often the case with jellies of this kind" (Thompson, 2004, p. 4). One hundred and forty-four has

probably never been the average number of tentacles the mature umbrella jelly has had. As Thompson acknowledges, Anscombe (1958) has made the same point about human teeth. We are often told that human beings have 32 teeth, but it certainly is not true that every human being has 32 teeth—some of us have more and some have less. Thirty-two is also not a statistical average for humans since the number of humans with fewer than 32 teeth is greater than the number with more. Nonetheless, it is true that humans have 32 teeth. It is also true that umbrella jellies have 144 tentacles. Each statement captures something that is true about each life form yet is not based on observational data.

Thompson's second example of how our reasoning about life forms extends beyond empiricism is about reproduction. If we compare the division of an amoeba and the division of a human cell we find that they have much in common. The chromosomes are copied, the nucleus splits in two, the cell's organelles arrange themselves symmetrically, etc. In each case, the outcome seems metaphysically mysterious. Olson, for example, has proposed that when an amoeba divides it ceases to exist:

> Clearly there are exactly two amoebas after the division, and the original amoeba cannot be identical with both. And nothing could make the original amoeba identical with one of its daughters but not the other, for its relation to each is the same. Neither does the amoeba become something other than an amoeba by dividing. Hence, it must perish. (Olson, 1997, p. 114)

Human cell division, as amoeba division, is equally metaphysically mysterious. When we study the pages of an introductory biology text, the essentials of both cell divisions are the same. But what is being reproduced in each case? Thompson thinks the *a priori* judgment reveals itself in the answer to that question, "while amoeba division is reproduction of amoeba-kind, human cell division is not the reproduction of humankind" (Thompson, 2004, p. 17). In other words, we do not think of the human kind as reproducing with each cell division but we do of amoeba kind. Once again, our judgment goes beyond empirical facts since there is nothing in the process of cell division that would lead us to this conclusion. Our application of the concept of reproduction is "everywhere implicitly mediated by an appeal to the underlying life form which the individual exemplifies" (Ibid.) According to Thompson, the fact that we appeal to the concept of a life form in order to draw conclusions about reproduction of a given kind, shows that our reasoning is not merely empirical but *a priori*.

The point of Thompson's two examples is to argue that the concept of a life form, including that of *Homo sapiens*, is not merely biological. That is not to say that Thompson is dismissive of the work of taxonomists. He acknowledges that they provide us with "a record either of history or of the similarities that the history explains" (Thompson, 2008, p. 67) but he nonetheless thinks that simply thinking of individuals in terms of life forms precedes any judgment of similarity or of a shared history. It is important to

keep in mind that Thompson is not interested in the metaphysics of life forms but in how we reason and come to various conclusions about them, "I think the question should not be: What is a life-form, a species, a *psuche*?, but: How is such a thing described?" (Thompson, 2008, p. 62) Thompson thinks that the way we talk about life forms reveals something about the way we reason about them. For example, the sentences used by the narrator of a nature documentary always take a particular form, "The S is (or has, or does) F" (Thompson, 2008, pp. 64-65). Thompson calls these judgments *natural historical judgments*, e.g., the umbrella jelly (S) has 144 tentacles (F). He thinks there is an important difference between the structure of these judgments and other types of judgment, e.g., "some S is F, all S's are F" and "most S's are F" or indeed "any S is F in normal circumstances, or ceteris paribus" (Thompson, 2008, p. 73). In the case of the latter type of judgment, F is attached to an individual variable as a property of individuals who belong to S. Conversely, what is expressed in natural historical judgment is a person's "*interpretation* or *understanding* of the life-form shared by the members of that class" (Thompson, 2008, p. 73).

Our language allows us to express natural historical judgments in slightly different forms, e.g., "S's are F" or "It belongs to an S to be F," but a common noun (S) and some predicative expression (F) are always present. Thompson thinks that the rest of the sentence, "the other linking expressions—the definite article, the bare plural—are part of the context"

(Thompson, 2008, pp. 64-65). His reference to context is, again, a reference to the *a priori* nature of natural historical judgments. When we make judgments about life forms we "look to a wider context" (Thompson, 2008, p. 55). If predators had destroyed the wings of a dragonfly or a sparrow so they were never actually used in flight, the left over stumps would still be wings. Why? Because judgments about wings are not judgments about the actual material constitution. Rather, the concept of a wing is "implicitly mediated by an appeal to the underlying life form which the individual exemplifies" [5] (Thompson, 2004, p. 17). Thompson makes a similar point about acorns. When we identify something as an acorn we do not make that judgment simply by looking at the material lump in front of us. By thinking of the acorn as a seed we have already "looked to a wider context." Hence, the look to a wider context is "not a look to the left and right." Instead, Thompson compares it to a "practice" in Rawls, where the description of an individual as "stealing a base" or "striking out" is available only given the practice of baseball (Thompson, 2008). While for Rawls, the wider context is a practice, for Thompson it is a life form.

Thompson thinks that within natural historical judgments there is a subgroup of judgments called judgments of natural goodness and badness.

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[5] Thompson is under the impression that identifying something as a wing is done by reference to *its particular life form*. However, this is not always the case. When a fossil is found and its life form is unknown, a particular body part may be identified as a wing, as opposed to a fin for example, by reference to *other life forms* with similar body parts.

Recall, that most judgments made by the narrator of a nature documentary take the form "The S is F" but some judgments—judgments of natural goodness or badness—might be about defects or deformities found in individual members of a particular life form. Given the proposition "The S is F" the narrator may infer "This S is defective in that it is not F" (Thompson, 2008, pp. 80-81). Here, she may show images of an individual jelly missing a tentacle or with a mouth that is malfunctioning. She may use words like "bad" or "defective" to describe this jelly. Such natural historical judgments are normative and it is the particular life form that sets the normative standard. The content of these judgments, unlike their form, may vary depending on life form. What counts as sound or defective in an umbrella jelly may differ from what counts as good or bad in other jellies, and still more in oak trees, bacteria, or tigers (Thompson, 2004). Moreover, judgments of natural goodness and badness about people, e.g., this person is imprudent, are simply judgments of soundness and defect as they apply to *our* particular life form, "The judgments in which I criticize the actions of individual persons as unjust or imprudent, or criticize the people themselves as unjust or imprudent people, will thus be special forms of what I called judgments of natural goodness or badness" (Thompson, 2004, p. 13). Judgments of natural goodness or badness are, thus, grounded in norms of behavior particular to each life form. I can judge my friend's actions to be good based on what it means for human beings to flourish but I cannot make the same judgment of

another species. For example, I cannot judge a praying mantis as bad for biting off her partner's head after mating, because human norms of behavior do not apply to nonhuman animals.

The fact that our judgments of natural goodness and badness do not apply to praying mantes is a point about scope. Thompson thinks that we rarely question the form of generality contained in our moral principles, e.g., "it is impermissible to do A" or "one has reason to do B" (Thompson, 2004, p. 15), but, in fact, the highest form of generality that can be attached to such claims is a life form. In humans, for example, when we criticize someone as unjust or imprudent we make a judgment about "the supposed goodness and badness of the operations of will and practical reason that would be exhibited in the action judged" (Thompson, 2004, p. 13). Thompson does not think such judgments apply across life forms, i.e., what is imprudent for one life form may be prudent for another, because what makes for a good will and a good practical reasoning is determined by the life form to which an individual belongs:

> Knowledge of what counts as a good sight, or as a sound capacity to move, is thus substantive knowledge of the specific life form in question…our fundamental practical evaluative knowledge is, as we have seen, substantive knowledge of what makes for a good will and good practical reason in a specifically human being. What would be a virtue in the bearers of another intelligent life form we don't know. We have no more insight into what would count as a 'reason for action' among Martians, for example, than we have into what would make for good eyesight among them, supposing they have eyes. The mind goes blank at the approach of the question. (Thompson, 2004, pp. 13-14)

It is not merely the case that standards of practical reason that apply to humans do not apply to nonhumans. Rather, it is that we cannot even make sense of what would count as a good reason for action for creatures of a life form other than our own (Kadlac, 2009).

This is where Thompson breaks away from the Kantian conception of practical rationality. Kant thought that moral principles are grounded in reason and thus, apply unconditionally to all rational creatures, regardless of life form:

> It may be added that unless we wish to deny to the concept of morality all truth and all relation to possible object, we cannot dispute that its law is of such widespread significance as to hold, not merely for men, but for all *rational beings as such*—not merely subject to contingent conditions and exceptions, but *with absolute necessity.* (Kant, 1964, p. 76)

Reason, for Kant, is the only thing that can transcend desire. Thus, the moral law, as it applies to rational beings, is not "subject to contingent conditions and exceptions." Rather, a morally good action is an action that we have reason to do regardless of what we happen to want, humans and nonhumans alike. "We ought never…to make principles depend on the special nature of human reason" (Kant, 1964, p. 79).

As Thompson points out, Kant thought that principles of sound practical reasoning applied indifferently to "humans, twin earthers, and Martians alike" (Thompson, 2004, p. 14). In contrast, Thompson, thinks that even if both humans and Martians could reason, and their reasons were

qualitatively the same, a human reason for acting would be different from a Martian's. He makes the same point about 'twin humans,' creatures "exactly similar to us, living on a planet, Twin Earth, that developed independently of ours, but that nevertheless came to be like Earth in any respect you care to mention" (Thompson, 2004, p. 12). Thompson thinks that these twin humans would be bearers of a different life form, even if we could not tell us and them apart. Given the differences in our life forms, our judgments of natural goodness and badness, as they apply to bearers of the human life form, would not apply to twin humans.

Thompson is opposed to equating the two life forms based on their material constitution—seeing as their material constitution is the same—because doing so would make the concept of a life form merely analytic:

> They are on all account properly 'twin humans', their form is not human form but twin human form. The anatomical, pathological, and cardiological textbooks published up there may say exactly the same things as ours do, and the diagrams may look exactly the same, but their treatises are speaking of and diagramming something else. Any other view would make the content of the treatises analytic. (Thompson, 2004a, p. 361)

How does one make sense of all of this? If twin humans and humans have all the same properties—insofar as we could not tell them apart—yet, at the same time, the concept of a life form is not analytic, what content are we to use for discriminating between life forms? For Thompson, the answer is the natural history of each life form. "The concept human…is a concept that attaches to a definite product of nature, one which has arisen on this planet,

quite contingently, in the course of evolutionary history" (Thompson, 2004, p. 12). An individual falling under the concept of red oak, Martian, human, twin human, etc., is always a matter of "falling into a single, naturalistically intelligible, trait-transmitting historical succession" (Thompson, 2004a, p. 366). This is the way in which we understand the category of a life form as it is found in nature, "a thing's coming under this form or universal arises through the operation of prior bearers of the form—that is, through reproduction or habituation" (Thompson, 2004a, p. 366). Thus, Thompson grants that the way humans turned out is a contingent fact of evolution, but he also argues that the way humans turned out is "no accident" at all, insofar as the human life form is a product of a specific shared evolutionary history, one that, by definition, could not have been shared with any other life form. Thus, for Thompson, normative judgments of the natural goodness or badness of a given characteristic will vary depending on the causal history of the life form to which the characteristic belongs.

John Searle's Argument for Causal Histories

Making a Moral Difference

I have now shown why Thompson thinks that causal histories should influence our moral judgment. Now, let me show why Searle agrees. Unlike Thompson, who is interested in comparing various characteristics across life forms, Searle is interested in comparing only one characteristic:

intentionality. Intentionality is a morally relevant characteristic because of its ties to autonomy. An individual cannot act of her own free will unless she can act intentionally. In a classic paper, Searle (1980) argues that computers, unlike brains, do not have "the right causal powers" for generating intentionality. What accounts for the difference between brains having intentionality and computers not having it, according to Searle, is not the formal structure of the brain—since the brain's organization could be paralleled in a computer—but the actual stuff that the brain is made of, e.g., neurons, axons, etc. "Whatever else intentionality is, it is a biological phenomenon, and it is as likely to be as causally dependent on the specific biochemistry of its origins as lactation, photosynthesis, or any other biological phenomena" (Searle, 1980, pp. 382-383). Searle grants that he might be the instantiation of a number of computer programs but, nonetheless, what allows him to have intentions is the fact that the programs are instantiated in an organism with a particular chemical and physical structure, "and this structure, under certain conditions, is causally capable of producing…intentional phenomena" (Searle). Only the right causal history, i.e., a biological one, can bring about intentionality:

> "Could a machine think?"
> The answer is obviously, yes. We are precisely such machines.
> "Yes, but could an artifact, a man-made machine, think?"
> Assuming it is possible to produce artificially a machine with a nervous system, neurons with axons and dendrites, and all the rest of it, sufficiently like ours, again the answer to the question

> seems to be obviously, yes. If you can exactly duplicate the causes, you could duplicate the effects. (Searle, 1980, p. 380)

Searle thinks that if two effects are identical, e.g., if both a human and a computer can pass the Turing test, we ought to judge the effects differently because of what gave rise to each one. If the cause were biological then the effect was intentional, otherwise it was not. What follows from this is that given the right causal history, a characteristic can be within the scope of moral judgment, otherwise it cannot.

Problems with Thompson's and Searle's Arguments

I have now shown why both Thompson and Searle think that the distinct causal histories of identical characteristics can rightly influence our moral judgment of each. However, I will now show why both of their arguments fail, and why changes to the causal history are morally irrelevant when these changes do not affect the moral characteristic in question. Thompson has argued that what makes for a good will and good practical reasoning extends only to individuals who share the same natural history, e.g., *Homo sapiens*. Now, to some extent I agree with Thompson. Insofar as our shared evolutionary history has had a profound effect on how we reason, it makes sense for him to say that the standards by which we judge an individual good or bad are species dependent. In other words, he is right to say that we do not extend our moral judgment to other species, e.g., praying

mantis, that do not share the evolutionary history that made us who we are today. The problem, however, is that proximate causes, such as gene mutations, can override the effects of a shared evolutionary history. For example, some humans are born with a severe mental handicap and thereby lack the ability to reason. Now, on Thompson's account, our judgments of natural goodness and badness should also extend to these individuals, since they are of the same life form as the rest of us. But how can we hold such individuals morally accountable for their actions, if they lack the capacity to reason? It seems to me that an individual who cannot reason, whether she is human or not, is beyond the scope of moral responsibility. If that is right, then contrary to what Thompson claims, the standards by which we judge an individual good or bad are not life form dependent. Rather, they depend on the mental capacities of the individual in question—regardless of what the causal history of that individual happens to be.

In contrast to Thompson, Searle's argument is prone to a different kind of objection. Although he successfully proves that a biological causal history is sufficient for intentionality, he fails to prove that it is also necessary. As Margaret Boden (1990) argues, Searle's analogy between intentionality and photosynthesis does not work, because while we can identify the products of photosynthesis and show how these differ from other biochemical products, our definition of intentionality is still philosophically controversial—we cannot even confidently identify it when we see it. Thus, Searle is right to say

that photosynthesis is causally dependent on the specific biochemistry of its origin, because "we not only *know that* chlorophyll supports photosynthesis, we also *understand how* it does (and *why* various other chemicals cannot)" (Boden, 1990, p. 92). Yet when it comes to intentionality, this thinking is not quite right. Why? Because intentionality is poorly understood; we hardly have a theory of it, let alone knowledge of how it is generated. Since we lack this kind of knowledge, we cannot successfully prove that biological causes are *necessary* for intentionality and consequently, Searle cannot be right. In sum, Searle's argument falls short of proving that a difference in causal histories amounts to a difference in our moral judgment of the effects.

Argument for Causal Histories Making a Moral Difference

Since neither Thompson nor Searle argue successfully for the conclusion that causal histories make a moral difference, thus far it looks like our moral judgment of Sagoff's mice should be the same regardless of any differences in their causal histories. In fact, to favor mice with the human cells simply because the cells are human would make us prone to Singer's "speciesist" objection. However, this does not mean that we should ignore causal histories all together. While Sagoff is right to point out that causal history is morally irrelevant to the *ontological* moral status of the animal, he does not point out that causal history is *epistemically* relevant to our ability to detect an animal's moral status. What I aim to show now, is that causal histories can be

morally informative when making a certain kind of inference—namely, an inference by analogy.

Arguments by analogy are often used to help solve the epistemological problem of inferring the mental states of others without having access to them. Since mental states are private experiences, and nonhuman organisms cannot directly communicate their mental states to us, arguments by analogy are used as a substitute. The arguments typically start with a premise about what we already know. For example, in humans we know that mental capacity X is correlated with the property (or set of properties) Z. Therefore, by analogy, if other organisms exhibit the property (or set of properties) Z, we can infer that they also have the mental capacity X. Typically, there are two types of properties invoked in arguments by analogy: behavioral properties or neurological properties. The following is an example of an argument by analogy that invokes behavioral properties. In humans, we know that the mental capacity to feel pain is correlated with a protective motor reaction. For instance, if we experience pain in our hand after an electric shock, we have a protective motor reaction to pull back our hand. By analogy, then, if we see a nonhuman organism pull back its appendage after an electric shock, we can infer that the organism also has the mental capacity to feel pain.

However, behavioral similarity can sometimes lead to false inferences. At the beginning of the 20th century, Charles Sherrington (1906) demonstrated that a protective motor reaction does not always provide

evidence that the animal is in pain. Sherrington transected the brainstem of animals, at the level of the midbrain, so that subcortical structures and the cortex no longer received input from the spinal cord. Although the forebrains of these animals were no longer receiving input from the periphery, behavioral responses to noxious stimuli were nonetheless observed. More recent experiments have shown that rats whose spinal cords are severed continue to respond to an electric shock applied to their hind legs (Grau, Barstow, & Joynes, 1998) and pinching the tail of a spinally transected cat will promote stepping movements of the hind limbs, demonstrating that simple escape movements can occur without pain (Lovely, Gregor, Roy, & Edgerton, 1986). Moreover, turning the head and neck toward the noxious stimuli, licking of affected paws and even vocalization can occur in decerebrate animals (Baliki, Calvo, Chialvo, & Apkarian, 2005; King, Devine, Vierck, Rodgers, & Yezierski, 2003; Sherrington, 1906).

In response to his findings, Sherrington coined the term *nociception* (from Latin *nocere* meaning "to harm"). Currently, nociception is defined as "the ability to detect a noxious, potentially tissue-damaging, stimulus and respond to it" (Elwood & Appel, 2009, p. 1243), while pain is "the associated unpleasant, emotional interpretation or feeling associated with the perception" (Elwood & Appel, 2009, p. 1243). To determine whether animals can experience pain, and not merely nociception, it is necessary to design experiments that bring out more than just behavioral responses to noxious

stimuli. Sharrington's discovery serves as a reminder that behavioral evidence is often inconclusive with respect to which mental capacity, if any, is associated with a given behavioral response.

Another type of inference by analogy that can help solve the question of whether other organisms have mental states relies on neurological rather than behavioral similarity between species. The structure of the inference is still the same: we start with a premise about what we already know and infer what is likely to be the case. For example, in humans we know that the mental capacity to feel pain is correlated with activation of the anterior cingulated cortex (ACC), i.e., part of the brain's pain network (Farah, 2008). Therefore, by analogy, if other organisms exhibit activation of the ACC, we can infer that they also have the mental capacity to feel pain. For example, experiments have shown that there are many similarities between human brains and rat brains, as well as similarities in the way their forebrains respond to noxious stimuli (cf. Apkarian et al., 2006; Borsook et al., 2006; Borsook et al., 2007). Other vertebrates, e.g., birds, reptiles, fish, etc. have spinal nociceptive circuitries similar to that of humans but they do not share the specific forebrain regions involved in human pain (National Research Council, 2009). Invertebrates share even fewer similarities. The idea, then, is that given some neurological similarities, or lack thereof, we can make inferences about the mental capacities of nonhuman organisms.

Nevertheless, using neurological similarity to make inferences about the mental states of others can be problematic for a few reasons. First of all, we do not yet have a complete understanding of the human brain. For example, recent experiments show that, in humans, the ACC can be activated by not only pain but also stimuli of which humans are unaware (Kilgore & Yurgelun-Todd, 2004; Sidhu, Kern, & Shaker, 2004). Second, structural similarity does not guarantee functional similarity, e.g., bat wings and human hands are structurally similar but they function in very different ways (Allen & Bekoff, 1997). Finally, if a brain structure associated with some mental state in humans, e.g., pain, is missing in another species, we may not be fully entitled to infer that the species is therefore incapable of that mental state. In other words, different structures may be associated with the experience of pain in different animals. For example, behavioral tests revealed that decapods have vision despite lacking a human visual cortex (Elwood & Appel, 2009).

In spite of these problems, Martha Farah (2008) argues that arguments by analogy that rely on neuroscientific evidence are more informative than ones that rely on behavioral evidence. The reason why is that the relations between mental states and brain states are "different in kind" from the relations between mental states and behaviors. For example, when my hand undergoes an electric shock, this causes me to feel pain, which in turn causes me to retract my hand. Hence, when I see a rat undergo an

electric shock and subsequently retract its legs I infer by analogy that the rat also feels pain. Here, the relation between the feeling of pain and retracting of the appendage is causal and contingent. Although it is likely that the pain from an electric shock will cause me to retract my hand, it is not certain that it will. After all, it is possible for me to act otherwise.

Conversely, Farah argues that the relation between the feeling of pain and my ACC activating is neither causal nor contingent. "The predominant view of the relation between mental states and brain states in cognitive neuroscience and contemporary philosophy of mind is one of identity: mental states *are* brain states" (Farah, 2008, p. 14). According to Farah, cognitive neuroscientists and philosophers of mind are in agreement that ACC activation is identical to pain and so it cannot exist without there being pain. Farah argues that even the people who hold the weaker version of this view would agree that if we know the ACC is activated in someone's brain, we also know that the individual is in pain. This connection, unlike the connection between mental states and behavior, is a necessary one. Because the relation between mental states and brain states is that of identity, and is therefore noncontingent, neuroscientific evidence is qualitatively different and more definite from behavioral evidence. Consequently, according to Farah, arguments by analogy that rely on neuroscientific evidence are more informative than ones that rely on behavioral evidence.

Thus far I considered two types of arguments by analogy used to infer the mental states of nonhuman animals: arguments that rely on behavioral properties and arguments that rely on neurological similarity. Now, I want to propose a third kind of argument by analogy that relies on genetic/cellular properties. To assess the mental capacities of a part-human organism, one might use the following argument by analogy. In humans, we know that mental capacity X is correlated with gene(s) or cell(s) Z. Therefore, if gene(s) or cell(s) Z are implanted into a nonhuman organism, we can infer that the organism will also express mental capacity X. Thus, for example, in humans we know that mental capacities are correlated with human neurons. Therefore, if human neurons are implanted into a nonhuman organism, we can infer that the organism will also express human mental capacities. Of course, Z and X can be more specific but the general idea is the same. What, then, is the relationship between genes/cells and mental capacities? First, genes and cells are not identical to mental states; rather, they can "give rise" to mental states via brain states. Hence, the relationship is a causal one. Moreover, the causal relationship between genes/cells and mental capacities, just as the causal relationship between behavior and mental capacities, is contingent. As I argued in the last chapter, depending on the circumstances, the transferred genes and cells may or may not give rise to a given mental capacity. In other words, there is no necessary connection between genes/cells and mental capacities.

Nevertheless, I take it that a weaker form of inference by analogy can still be used to draw conclusions about the mental capacities of part-human organisms. The argument might look something like this. In humans, we know that mental capacity X is correlated with gene(s) or cell(s) Z. Gene(s) or cell(s) Z are implanted into a nonhuman organism. The nonhuman organism is more likely to also have mental capacity X—at least more likely than if the gene(s) or cell(s) Z came from an organism that lacks mental capacity X. Hence, if we know that the genes or cells transplanted into a mouse came from a human who has evolved the capacity to reason, then we can infer that the mouse is more likely to also acquire the capacity, at least more likely than a mouse who receives genes or cells from an animal that lacks the capacity. Now, this argument is somewhat weaker than arguments by analogy that rely on neurological or behavioral evidence. Nonetheless, I believe it should still inform our judgment regarding the moral status of part-human organisms. Here is how.

Previously, I established that moral status is attached to mental characteristics. From this I concluded that if the morally relevant characteristics of Sagoff's mice are identical, then the moral status of the mice should be the same, regardless of how the characteristics were acquired. Unfortunately, however, it is not always easy to figure out who has and does not have morally relevant characteristics. Consider a spectrum: at one end are morally relevant capacities that are easy to test for, at the other end are

morally relevant capacities that are very difficult to detect. Pain, for example, might be at the "easy" end of the spectrum. Of course, even pain is not so easy to detect since behavioral cues may be a sign of nociception rather than pain. However, as I mentioned previously, invasive experiments may be conducted to rule out one or the other. Conversely, the "hard" end of the spectrum might contain morally relevant capacities that are almost impossible to detect, e.g., intentionality. If an individual claims that she intended to do something but then fails to do it, it is very hard to determine whether she failed to have the intention or whether she failed to have the will to carry out what she intended to do.

The point, then, is that knowing whether the implanted genes or cells came from an individual who has evolved some "hard" to test for capacity may help us make more accurate judgments regarding that organism's moral status. After all, the relationship between genes/cells and mental capacities may be contingent but it is nonetheless causal. Hence, if a cell that was implanted into a mouse came from an elephant that we know has the capacity to feel empathy (see for example Bates et al., 2008), and if it turns out that empathy is a morally relevant capacity that is difficult to test, then we should take this into consideration when making judgments about the moral status of the mouse. On the other hand, if the cells implanted into a mouse came from an organism that we know lacks the capacity to feel

empathy then, again, that consideration should influence our judgment of the moral status of that mouse.

In sum, the causal history behind an acquired characteristic of a mouse may be epistemically *morally relevant* because it can provide evidence about what inferences are justified regarding the acquired characteristic. This is in contrast to Sagoff's earlier point. Nevertheless, Sagoff is right to say that causal history is *morally irrelevant* to the ontological moral status of the animal. Given this distinction in the role of causal history in informing our moral judgments, we can conclude that the origin of cells implanted into an organism can make a difference to our judgment of the organism's moral status.

Summary

I started this chapter with a literature review of arguments made by ethicists troubled by the possible creation of mice with human characteristics. The worry of these ethicists is that conferring humanity onto mice might entitle them to an upgrade in moral status. But holding such a belief makes one a speciesist, according to Singer. Singer is opposed to giving preferential treatment to humans over nonhumans and instead favors a version of the person/nonperson view of moral status. On this view, a person is someone with characteristics that we believe to be morally relevant, e.g., the ability to feel pain, and insofar as one has these characteristics, one can be a person

even if one is not human. Given this distinction, it may seem that a proponent of the personhood view would find the humanness of part-humans irrelevant to how we ought to judge their moral status. After all, if being human does not matter for being a person, why care about how human something is? This is the problem Sagoff has raised. Is the causal history of an acquired characteristic, e.g., whether it came about as a result of a dolphin or a human transplant, morally irrelevant? Although Thompson and Searle have argued in favor of causal histories making a moral difference, I found neither of their arguments convincing. Consequently, I argued that causal history is morally irrelevant to the *ontological* moral status of the animal, but *epistemically* relevant to our ability to detect an animal's moral status.

CHAPTER 7

CONCLUSION

I want to end with a summary of the dissertation. I began with a brief history of xenotransplantation and showing that the idea of improving or prolonging life by replacing body part has a long and interesting history. For example, people used to believe that the qualities of one individual can be transferred to that of another through the exchange of blood. In Chapter 2, I offered an account of various transplantation experiments, starting with sheep blood transfusions of the 17th century, continuing to frog tissue grafts of the 19th century, and finally ending with ape testicle and organ transplants of the 20th century. Towards the end of the 20th century, the techniques used to transplant parts across species changed dramatically. Although scientists still work on improving the transplantation of blood, tissues and organs, the main focus of xenotransplantation shifted to genes, chromosomes, nuclei and eventually stem cells.

In Chapter 3, I explained how modern part-humans are made. I focused on four candidates: chimeras, hybrids, cybrids and transgenics. To

recap, chimeras contain cell populations derived from at least two different zygotes of the same or different species. Currently, there are a few different ways to create human-nonhuman chimeras. First, human tissues and organs can be engrafted onto immunodeficient nonhuman animals—e.g., human tumors in Nude mice. Second, nonhuman organs can be transplanted into humans. However, since nonhuman organs tend to be rejected by humans (with or without immunosuppressant drugs) it is best to "humanize" the nonhuman donor before transplantation in order to prevent rejection. Last, nonhuman cells can be engrafted onto humans—e.g., porcine neurons in the brains of Parkinson's patients—and conversely, human cells can be engrafted onto nonhuman animals—e.g., human neurons in the brains of old world monkeys.

Unlike chimeras, hybrids are made by mixing gametes, i.e., sperm and egg, of two different species. No human-nonhuman hybrid was ever created, but human-nonhuman fertilized eggs have been created to test the fertilization capacity of human sperm, known as the "hamster test." Yet another part-human candidate is the cytoplasmic hybrid, or cybrid, made by inserting a nucleus of a somatic cell of one species into an enucleated egg of another species. An enucleated egg lacks a nucleus but contains its own cytoplasm and mitochondrial DNA. Although scientists have attempted to make human-nonhuman cybrids by injecting human nuclei into enucleated rabbit cells, the cybrid embryos did not develop past the blastocyst stage.

Finally, transgenics are made by splicing sequences of foreign DNA into the recipient's genome. Human-nonhuman transgenics are usually created for medical purposes, e.g., to secrete human proteins in their body fluids or to mimic human diseases.

The next two chapters were dedicated to the central question of my dissertation. Are the above listed candidates part-human or merely partially composed of human parts? The reason why it is important to establish the exact humanness of these animals is that various ethical and legal regulations are based on the human/nonhuman distinction, e.g., patenting regulations and regulations for conducting research on human and nonhuman subjects.

In Chapter 4, I looked at some of the ways in which philosophers have thought about parts and wholes to see if any of the available part/whole distinctions can help to distinguish animals partially composed of human parts from animals that are part-human. I started with mereology—a metaphysical theory of the relations between parts and wholes, and argued that it is not equipped to capture the variable and complex nature of organisms because of its ties to set theory. Similar to set theory, mereology has an Extensionality principle, which states that an object is exhaustively defined by its constituent parts. However, contrary to this principle, an animal is identical with itself even though it gains and loses parts in the course of its life, and an animal is not identical to its disassembled parts,

because, contrary to the Extensionality principle, the arrangement of parts is relevant to identity.

Next, I looked at bio-ontology, which is an applied form of standard mereology designed to capture the variable and complex nature of biological entities. However, I was disappointed to discover that bio-ontologists treat species as classes that have law-like relations, their criteria of parthood are undeveloped, and their account of function is questionable. In the next section, I considered an intuition-based approach to parts and wholes, an approach that is used not only in mereology/bio-ontology but also in bioethics. I found two problems with the intuition-based approach. First, evidence from psychology suggests that when it comes to judging the relative humanness of part-human hybrids, our intuitions run contrary to our reasoning; and second, human intuitions often mislead us when we rely on them to make judgments about empirical facts.

Towards the end of Chapter 4, I examined two part/whole distinctions often used to help categorize biologically engineered animals. The first was the quantitative approach, by which the degree of humanness is calculated via the ratio of human to nonhuman parts. I concluded that this approach is unlikely to be a good measure of the level of humanness found in any animal because of the surprising ratio of human to nonhuman cells in a typical human body, the high number of conserved genes among animals, and the complicated relation between organic wholes and their parts. The second was

the germ-line/soma distinction, an approach that emphasizes placement instead of number of human parts in the genetically engineered animal. The problem with this approach, however, was that while the germ-line/soma distinction may be well suited for examining the humanness of the offspring of modified animals—if the animals reproduce at all—it is not well suited for examining the humanness of modified animals themselves.

Finally, in Chapter 5, I provided an approach that involves establishing the minimum that is required for an animal to count as part-human. I argued that whether an animal is part-human or merely partially composed of human parts depends on the transposability of parts. A suitably transposable part is characterized by its giving rise to the same characteristic in both recipient and donor. I argued that a part is transposable across species if the following three requirements are met: 1) the right partitioning frame is chosen 2) part-boundaries are correctly identified and 3) contextual constraints are eliminated. The first two requirements ensure that the parts chosen for transfer in the human, e.g., human genes, chromosomes, cells, etc. are the ones that give rise to the target phenotype, e.g., Down syndrome. The last requirement ensures that differences between donor and recipient that could prevent transferred parts from giving rise to analogous traits in the recipient are eliminated. In the first three sections, I demonstrated the force of each requirement with examples from current research and argued that if they are met, the animal has part-human potential. In the last two sections, I

considered possible objections to my argument and demonstrated the broad scope of my requirements.

The requirements I offered in Chapter 5 have obvious practical applications. Research ethics committees and members of the Patenting Office can use my requirements to set aside submissions that involve animals partially composed of human parts, so that they can dedicate more time to the part-human candidates. However, my requirements are only useful insofar as our ethical and legal regulations give preferential treatment to humans over nonhumans. Yet, many ethicists—most famously, Peter Singer—have argued against the human/nonhuman distinction. Ethicists who oppose giving preferential treatment to humans over nonhumans tend to favor some version of the person/nonperson distinction, where a person has moral status in virtue of having characteristics that we believe to be morally relevant, e.g., the ability to feel pain, the ability to reason, etc. My aim in Chapter 6 was to consider the moral status of part-human animals from the standpoint of someone who holds the person/nonperson distinction instead of the human/nonhuman distinction. While it may seem obvious that a proponent of the personhood view ought to find the humanness of part-humans irrelevant to how we ought to judge their moral status, I argued that this need not always be the case. Whether a morally relevant characteristic came about as a result of a human rather than a dolphin transplant can make a moral difference. In particular, although causal history is morally

irrelevant to the *ontological* moral status of the animal, I argued that it is *epistemically* relevant to our ability to detect an animal's moral status.

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